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.

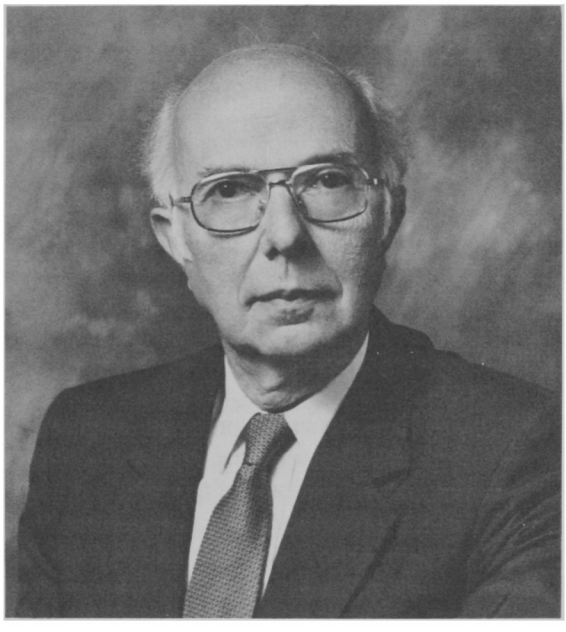
Studying oncogenes and tumor viruses could not, however, fully explain the "progression" of tumors—the multiple steps along the road from normal cell maturation to proliferation to cancer. Changes in genes were obviously taking place on this journey, but they could not be easily followed for lack of 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.

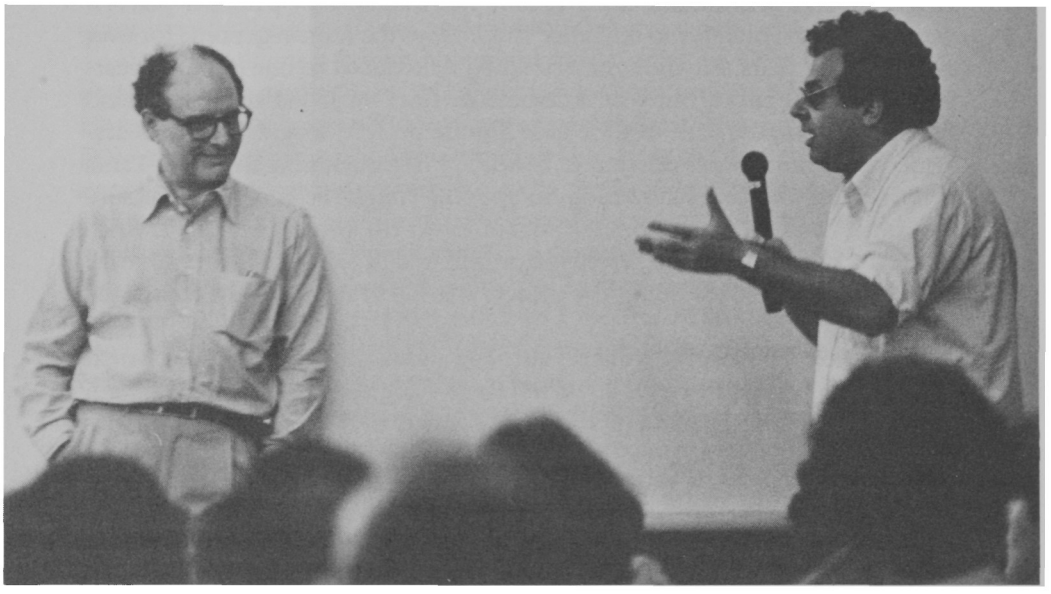
Berg led off by trying to channel discussion into the scientific merits of mapping and sequencing, and what technical approaches might make the effort feasible. Gilbert briefly described the Santa Cruz and Santa Fe meetings

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.

PART THREE

The Support Structure

9

The Odd Legacy of Howard Hughes

THE HOWARD HUGHES MEDICAL INSTITUTE (HHMI) was founded on December 17, 1953, six months after Watson and Crick published their double-helical structure of DNA. In an irony of American capitalism, the largest biomedical research philanthropy in the United States was founded as a tax dodge for a defense contractor.

Howard Robard Hughes, Jr., set the institute up a week before his forty-eighth birthday. He apparently had ideas about establishing a medical research institution of some kind as early as 1926, according to George Thorn, who was the institute's scientific director from 1956 to 1978.[1; 2] Planning got more serious in 1946, when Hughes commenced discussions about a medical institute with his personal physician Verne Mason. Hughes was then recovering from injuries sustained in the crash of a prototype XF-11 photoreconnaissance plane he was test-piloting. He was, perhaps, feeling especially appreciative of modern medical technology and its scientific underpinnings and may have been thinking about what sort of legacy to leave behind.[3] In 1950, Hughes gave a total of $100,000 directly to the first three Howard R. Hughes Fellows; he funded another four in 1951.[2]

The institute was created as part of a legal package that carved the Hughes Aircraft Company out of the Electronics Division of Summa Corporation.

Summa was part of the original Hughes Tool Company, an oil-drilling-equipment company which Howard Hughes inherited from his father at age nineteen. In late 1953, Hughes was under intense pressure from his chief client, the U.S. Air Force, to make management improvements or risk losing future business with the government.[4] The reorganization was the result. The medical institute was given ownership of the Hughes Aircraft Company, a part of the larger Hughes conglomerate. Hughes himself was sole trustee of the institute from its founding until his death on April 5, 1976. During those twenty-three years, the institute spent $63 million for medical research.[2]

The charter of the new institute stated:

> The primary purpose and objective of the Howard Hughes Medical Institute shall be the promotion of human knowledge within the field of the basic sciences (principally the field of medical research and medical education) and the effective application thereof for the benefit of mankind.[3]

The Internal Revenue Service begged to differ. In November 1955, the IRS concluded that the institute was "merely a device for siphoning off otherwise taxable income to an exempt organization and accumulating that income."[4] The IRS denied tax-exempt status to the institute until March 1, 1957, when it was granted. (In the meantime, Hughes underwrote a loan to Donald Nixon, brother of the Vice President and future President. The loan was never repaid, although no connection to the IRS approval of tax-free status was established.)[4]

The institute dramatically increased both the number of investigators and its financial commitment to them, beginning in 1976, in response to a report from its medical advisory board. Hughes, the sole trustee, died that year. Before he died, the institute had already chosen to focus on three fields believed fundamental to understanding human disease: genetics, immunology, and the study of metabolic-endocrine disorders.[3] In 1976, the institute's spending increased dramatically to $4.7 million, and by 1980 it reached $25.8 million.[5] An important new element was support of research itself, in addition to payment of the investigators' salaries. Until then, at Hughes's direction, only salaries had been paid by the institute.[6]

In 1984, the Delaware Court of Chancery removed management of the institute from its executive committee, which had run it during the eight years of litigation following Hughes's death. The reins were handed to an eight-member board of trustees appointed by the court. The trustees elected a ninth member later that year. Donald S. Fredrickson, who had directed the National Institutes of Health from 1975 to 1981 and joined HHMI as vice president in 1983, was appointed president.

Early in 1985, the trustees decided to sell Hughes Aircraft. The sale was prompted by the tax dispute with IRS that had hounded the institute for more than two decades. Fredrickson explained, "We could not settle this controversy with the IRS without knowing the exact worth of our endowment, and the

only way to do that was to sell the company."[7] Hughes Aircraft was put on the auction block, and General Motors bid highest. GM paid HHMI $2.7 billion in cash and created 100 million shares of a special stock valued at roughly the same amount. The GM settlement was itself a source of friction until a February 1989 agreement between GM and Hughes.[8;9] The sale of Hughes Aircraft made HHMI the largest private philanthropy in the nation, with assets then valued at $5.2 billion.

From 1985 through 1987, as the genome debate was intensifying, HHMI was in the throes of managing its explosive growth. Its research budget more than doubled from 1985 to 1986, reaching $214 million, with another $17 million for administration.[5;10] On March 2, 1987, the institute reached a settlement with the IRS, ending the tax dispute.[11] HHMI agreed to spend 3.5 percent of its endowment in support of research each year, to pay the U.S. government $35 million to forgive any tax obligations it might not have met (although not admitting to any), and to give out at least an additional $500 million for special projects related to the HHMI mission over the next decade (ending August 1997).

The tempest of controversy was not quite spent. Donald Fredrickson took a leave of absence in April 1987 and resigned as president on June 2. His highly publicized forced resignation was viewed as "both a personal tragedy and a public loss."[12] He left amid allegations that his wife had improperly wielded authority over renovations of an HHMI property located on the NIH campus. The HHMI trustees had voted to bar Mrs. Fredrickson from HHMI meetings in December 1986 and hired a firm to investigate HHMI financial dealings. They got back a report of more than three hundred pages that did not find conclusive proof of wrongdoing, but convinced the trustees that decisive action was necessary.[12;13]

The institute continued to consider action on the genome project amid all the turbulence caused by selling Hughes Aircraft, planning what to do with its newfound wealth, negotiating a settlement with the IRS, and losing a president. The science went on, and HHMI played a pivotal role in the genome debate.

The HHMI interest can be followed along several paths. HHMI staff credit Ray Gesteland and Charles Scriver as the people principally responsible for getting HHMI interested in gene mapping. Gesteland was a student in the Watson laboratory in the mid-1960s and later became an independently supported Howard Hughes Investigator at the University of Utah. Soon after publication of the RFLP mapping paper in 1980, Gesteland suggested to George Cahill, then HHMI's director of research, that HHMI might support systematic RFLP mapping along the lines proposed by David Botstein at MIT. Botstein had independently raised the idea of RFLP mapping with HHMI trustee George Thorn.[14] Ray White, still at the University of Massachusetts at Worcester, had by then contacted David Botstein about RFLP mapping.

Cahill recruited White to go to Utah.[15] In the background was a desire among some HHMI trustees to strengthen ties to Salt Lake City, because of Howard Hughes's Mormon connections. White was attracted in part because of the incredibly rich and detailed Mormon pedigrees kept by the university that might be useful for clinical genetic studies. The large and well-documented families were a unique resource. They would be invaluable not only in the search for RFLP variants, but also for disease-gene mapping once the markers were in place. White commenced work to construct a genetic linkage map when he moved to Salt Lake City in November 1980, building on his recent success in finding the first RFLP marker with Arlene Wyman.

Scriver was a Canadian geneticist of international reputation serving on the HHMI medical advisory board from the late 1970s into the mid-1980s, a period during which the institute's annual funding for biomedical research increased more than twenty-fold. Scriver was fascinated by the prospect of a Human Genome Project, thinking primarily of the immense impact systematic mapping could have on medical genetics. He was concerned about science, but also about the patients he saw every working day in his Montreal genetics clinic. He called the decision to fund genetic linkage mapping, for which he became a champion on the medical advisory board, "a close thing" on the part of HHMI. Several years later, the trustees and scientific advisers to HHMI considered this among their most productive investments.[16]

Scriver became convinced that support of genetics databases was an essential next step, mainly through conversations with Frank Ruddle of Yale, and later with Ray White. Scriver worked to persuade the other members of the medical advisory board. He spoke three times at board meetings. The first two times, he sparked little enthusiasm; by the third meeting, however, George Cahill had warmed to the idea and supported an HHMI commitment. Scriver then made a presentation to the trustees in December 1985. He caught trustee Hanna Gray's attention by referring to how genetic maps would introduce a neo-Vesalian era into medicine. (The Flemish anatomist Andreas Vesalius prepared diagrams based on actual dissections in the mid-1500s. His methods were not universally applauded—indeed, they were regarded as sacrilegious and macabre by many at the time. His anatomy paved the way for the functional studies of William Harvey in England a century later, and the Italian Giovanni Morgagni's studies of how disease affected the body in the mid-1700s.) The trustees agreed to support genetic database efforts for five years, from 1986 to 1991, subject to annual review.

Having secured trustee approval, Scriver, Cahill, and Fredrickson convened a special meeting to discuss the HHMI human genetic resources at HHMI headquarters in Coconut Grove, Florida, on February 15, 1986. (Headquarters moved to Bethesda, Maryland, in 1987.) Fredrickson opened the meeting, followed by Scriver. Next were presentations from the Utah human genetics team and the New Haven group that ran the Human Gene

Mapping Library. The focus was on how to manage the massive increase in information about genetic marker maps, locations determined by somatic cell genetics, and new DNA probes. There was also much discussion of the emerging broad outlines of the genome project, particularly its underlying technologies.

The Coconut Grove meeting took place two weeks before the DOE meeting in Santa Fe on sequencing the genome, but the two meetings were in separate orbits. Ruddle was central to both efforts, but his was one of the few areas of overlap, and the emphases of the two discussions were quite different. DOE concentrated on sequencing, viewing physical mapping and genetic linkage maps as steps along the way. HHMI had a major commitment to genetic linkage mapping, supporting the largest group in the world, and was moving toward support of databases. The initiatives converged only later under the umbrella of the Human Genome Project. In March 1986, the emerging HHMI interests and DOE's nascent genome initiative were worlds apart. In June, attention shifted to the contretemps at Cold Spring Harbor. In July, the HHMI and DOE programs were brought face to face at an HHMI public forum, Washington's first major public event dedicated solely to the genome project.

After the Coconut Grove confab, HHMI wanted a much larger and more public forum on genome research. The July meeting was scheduled to prepare Fredrickson for another HHMI trustee meeting on August 5. Maya Pines, a professional science writer, was commissioned to describe gene mapping and sequencing to the HHMI trustees. Genetics was HHMI's strongest research area, constituting roughly a third of its research. HHMI polled its contacts about what its role should be. James Watson met with Fredrickson on April 1 to indicate his strong support for an HHMI presence in genome research.[23; 24] While DOE came to human genetics mainly form technology—laser-activated sorting of chromosomes, DNA sequence database experience, and projects to make clone libraries of the different human chromosomes—HHMI was smack in the middle of mainstream human genetics, supporting many of the most prestigious groups in the world. As a consequence, HHMI drew on an international constellation of stars for its July forum.

In the wake of Cold Spring Harbor, there was a palpable tension surrounding the HHMI forum. The stage was set; science journalists and others interested in science policy flocked to watch the sparks fly. It was a gala event held on the NIH campus, July 23, 1986. Sinsheimer, Watson, Gilbert, and Lloyd H. (Holly) Smith (chairman of the HHMI medical advisory board) sat next to one another cribbing notes in the Nobel laureates' corner, next to the dean of human genetics, Victor McKusick. Donald Fredrickson, former director of NIH and then president of HHMI, introduced and closed the meeting, which was chaired by Walter Bodmer from the Imperial Cancer Research Fund laboratories in London.

The HHMI forum turned into a love fest for a redefined genome project. There were several brief presentations about the technologies and what was going on in U.S. agencies and in other parts of the world. But mainly, it was a show of power—a battleship summit for molecular biology. The HHMI forum was a turning point, but the new direction was not entirely clear at the time. *Science* reported that "the drive to initiate a Big Science project to sequence the entire human genome is running out of steam."[17] Leroy Hood asserted that massive sequencing was premature, and that the focus should instead be on improving the technologies.

Under the surface, however, a new consensus was emerging. The meeting rechanneled the genome project, rather than rejecting it outright. Those attending the meeting agreed that the time was ripe to mount a special initiative in gene mapping and technology development, to redress deficiencies in the infrastructure undergirding genetics. This agreement was obscured by more conspicuous disagreements about priorities and the proper style of leadership. At one critical juncture, chairman Bodmer could not contain himself when David Smith presented an outline of the DOE genome initiative. Bodmer interjected that the DOE proposal did not acknowledge the importance of genetic mapping. While Smith continued, a bit shaken, Sydney Brenner, seated at the meeting table, conspicuously passed a note to Gilbert and Watson that was read by those around them: "This is a retreat."[18;19] DOE was on hostile turf, in the homeland of NIH and HHMI.

A two-phased strategy emerged from the HHMI forum. The first phase would concentrate on genetic linkage mapping, physical mapping, and development of technologies for DNA sequencing and for analyzing genetic information with computers. The second phase, contingent on reassessment as Phase I progressed, would concentrate on DNA sequencing. This could aim to sequence the entire human genome or not, but it would clearly start first with genes and regions of interest. Leroy Hood urged that the emphasis fall on developing new technologies during the early years, so that later efforts would be faster and more efficient.

James Watson allowed that while he was strongly in favor of a genome project, everyone else he talked to at Cold Spring Harbor Laboratory was against it.[17] He reflected that young scientists feared a massive sequencing project might subtract from the pot of funds available for their work,[17] but he pointed out that the mapping work deserved special attention or it would not get done. "We know how useful this Phase I work is. There should be more of a sense of urgency about it. Are we going about it as if we were in a war?"[20]

Walter Gilbert added a Phase III, understanding the function of the genes uncovered in Phases I and II. In Gilbert's mind, Phase I would last five years or so, Phase II a decade, and Phase II would be much of biology in the twenty-first century. Walter Bodmer summed up his sense of the meeting by focusing on the primary goal of the genome project: understanding human disease. There were subsidiary goals related to understanding evolution and variations

among different populations, but the central thrust of the project should be to expedite all biomedical research.[17;20;21]

After the Coconut Grove meeting and the July forum, HHMI moved on several fronts. Maya Pines completed her briefing paper for the trustees, *Shall We Grasp the Opportunity to Map and Sequence All Human Genes and Create a "Human Gene Dictionary"*?[20;22] The answer was clear; "the monumental project of mapping the entire human genome has moved from a pipe dream to a realistic goal which is arousing increasing enthusiasm."[20] HHMI proceeded to fund several international human gene mapping workshops, where geneticists from around the globe assembled to hammer out the best maps of various genes and RFLP markers. HHMI also directly funded the on-line version of McKusick's *Mendelian Inheritance in Man* at Johns Hopkins, carrying forward work previously supported by the National Library of Medicine. HHMI picked up funding of the Human Gene Mapping Library in New Haven from NIH from 1985 to 1989. During 1988 and 1989, HHMI convened a special review panel to chart the future of genome databases. The committee advised HHMI to phase out the Human Gene Mapping Library in favor of a new Genome Database, to be developed by Peter Pearson, Richard Lucier, and staff of the Welch Medical Library at Johns Hopkins. HHMI also supported a parallel effort to computerize a genetic database for mouse genetics at Jackson Laboratories in Maine. HHMI gave funds to the Centre d'Etude du Polymorphisme Humain (CEPH) in Paris to support the international collaboration unifying genetic linkage mapping efforts around the world.

HHMI support of databases and international collaborations knitted together a disparate and widely dispersed genetics community, weaving an informal network of electronic and personal ties. Finally, HHMI commissioned Maya Pines to write a public document describing the genome project. This booklet was released in December 1987, as Congress was preparing for the 1989 budget, and as prospects for the future of the project in Congress were still unclear.[25]

Hughes also lent support as a new scientific organization, the Human Genome Organization, formed to mediate international collaborations. Agreement to form HUGO, as it was soon nicknamed, came from an impromptu meeting called by McKusick at the first annual Genome Mapping and Sequencing Symposium at Cold Spring Harbor on April 29, 1988. HHMI paid for the thirty-two founding members from eleven nations to meet in Montreux, Switzerland, in September. Early in 1990, HHMI agreed to give HUGO a $1 million startup grant for four years. Diane Hinton of the HHMI staff was appointed administrator of the Americas office for HUGO. HHMI housed HUGO in the United States for several years, and in November 1990 donated a Bethesda, Maryland, office condominium owned by HHMI to HUGO for its use.

HHMI moved decisively to support genome research at several points. It established the first and largest RFLP mapping effort soon after the idea was

published. It moved to support several computer databases for human and mouse genetic information. And it helped to establish HUGO as the international coordinating body. HHMI also played a more informal role in the interagency jockeying that took place as the genome project unfolded. George Cahill and Diane Hinton emerged as central mediating figures. After Cahill retired, Max Cowan assumed his position as a major coordinator and funder of genome research internationally. HHMI was presumed to be a neutral party in most disputes, a philanthropy with international reach and a commitment to shared informational resources in human genetics. HHMI was smaller than the federal agencies, but large enough to sustain significant commitments of money and personnel. It responded rapidly when federal agencies did not, filling niches left vacant by the NIH behemoth. Howard Hughes had his name, however inadvertently, on the flight of the genome project as it lifted off the runway a decade after his death.

10

The NAS Redefines the Project

THE JULY 1986 HHMI forum began a several-year period during which the National Institutes of Health and the Department of Energy jousted over the genome project. Indeed, which agency would prevail became the dominant topic of discussion about the genome project until well into 1988. Only then did an emerging consensus about the importance of a concerted research effort begin to displace divisive debates over who would get to run it.

At the July 1986 Howard Hughes Medical Institute forum, the question imperceptibly shifted from the central focus of the Cold Spring Harbor meeting. Whether to start a genome project gave way to what it encompassed, how best to do it, and who should lead it. By the end of 1986, it was already clear that DOE was committed to mounting a genome project and HHMI would play a small but significant part. The big question was what would happen at NIH.

The consensus was not yet apparent, however, and having an endorsement from a single meeting convened by HHMI was not necessarily politically persuasive. HHMI was already committed to genome research, and the most prominent skeptics—such as Maxine Singer and David Botstein—were not at the HHMI forum. A more formal scientific review was necessary before the genome project could be said to command a scientific consensus. The natural body to perform this function was the National Research Council of the National Academy of Sciences.

President Lincoln signed legislation creating the National Academy of Sciences on March 3, 1863, during the Civil War. The Academy was the brainchild of Alexander Dallas Bache, who in 1851 first proposed a national scientific body to rival the French Academy and the British Royal Society. Language for the bill came from a Saturday-night dinner meeting on February 19, 1863, that included four members of an informal scientific group called the Lazzaroni. Louis Agassiz, an eminent natural historian from Harvard, interested Senator Henry Wilson of Massachusetts in sponsoring a bill, which was introduced on February 21 and passed well after seven in the evening of the last day of the legislative session, without a complete reading and with no

debate. The legislation listed the initial fifty scientist members, designated by those at the February 19 meeting. Bache became the first president, but his health soon declined and with it the Academy's. The Academy was rescued from lassitude by the eminent physicist (and head of the Smithsonian Institution) Joseph Henry, behind whose back it had been created. Despite being excluded from the negotiations to create the Academy, Henry stepped in to direct it. He put it on firm footing by getting Congress to permit an expansion of membership and by focusing its energies on basic science.[1] The enacting legislation decreed:

> The Academy shall, whenever called upon by any department of the Government, investigate, examine, experiment, and report upon any subject of science or art, the actual expense of such investigations, examinations, experiments, and reports to be paid from appropriations which may be made for the purpose, but the Academy shall receive no compensation whatever for any service to the Government of the United States. [An Act to Incorporate the National Academy of Sciences, 37th Congress, Session 3, Chapter 111, March 3, 1863]

In 1916, the astronomer George Ellery Hale and a committee he chaired wrote to President Wilson, offering the services of the National Academy of Sciences and urging the establishment of a National Research Council (NRC) to provide advice to the government. American involvement in World War I was looking more and more likely, and scientists saw a great opportunity to further the war effort if a broader scientific body were to become more actively involved with providing advice than the Academy itself. The National Research Council could involve scientists who were not members of the Academy, greatly expanding the range of available expertise. The president accepted the Academy's invitation, and the NRC had its organizational meeting in September 1916. Hostilities with Germany broke out in 1917, and the NRC busied itself, under the direction of physicist Robert Millikan, with fundraising and organization to help the war effort. After the war, an executive order of May 11, 1918, made the NRC permanent, and it began to dispense funds from the large private foundations. In this period, the NRC "so nearly lost touch with the federal government that it was neither a coordinating center for science in the bureaus nor an active adviser," according to one historian.[1]

Relations between the National Academy of Sciences, its NRC advisory arm, and the federal government waxed and waned. In general, during times of war, science came closer to government, but then it drifted away in times of peace, until after World War II. In the postwar period, the permanent federal commitment to science grew substantially as the links among science, technology, military power, and economic growth became widely held cultural beliefs. It was not always so. A Colorado congressman commenting on the Academy in the late 1870s quipped:

> This Academy has never published but one work, and that was a very thin volume of memoirs of its departed members. And if they are to continue to engage in practical

legislation, it would have been well for the country if that volume had been much thicker.[1]

Such sentiments ebbed to a small minority as science and technology become more central to national life. The National Academy Complex, which to the Academy proper and the NRC added a National Academy of Engineering in 1964 and the Institute of Medicine in 1970, had an annual budget of roughly $160 million by the end of the 1980s. In any given year, a thousand committees worked on various projects, with the federal government supplying more than three-fourths of the total funding.[2;3]

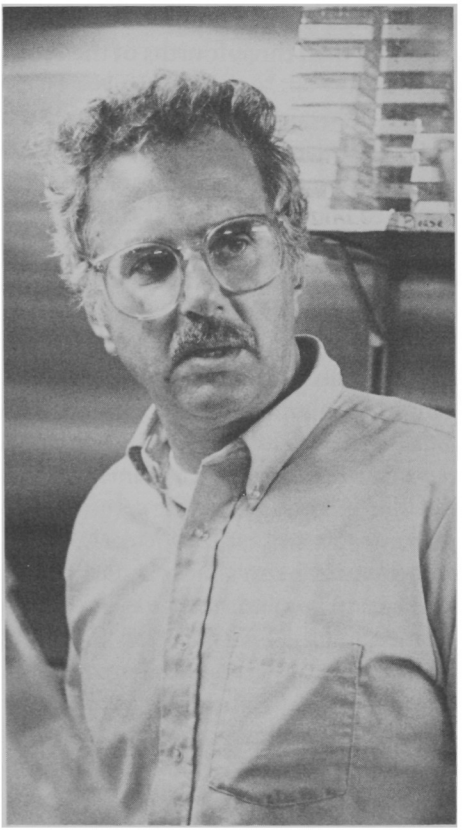
In 1986 and 1987, debate about the wisdom of mounting a genome project was largely confined to the scientific community and was of particular interest to geneticists and molecular biologists. The pro and con arguments began to converge on what should be done and how to do it, questions well suited to the report-writing process employed by the NRC. The NRC process ensured a systematic assessment often absent from open-ended debate. A report from the NRC also carried special weight in Congress and in executive agencies.

Convening a panel on the genome project was a considerable risk for genome proponents at the time, because sentiments were largely against the DOE proposal, which had dominated discussion to that point. An NRC report that equivocated or came out against a genome project would likely kill the idea in any agency, for several years at least. A positive report would not guarantee its success, particularly if it asked for extra funding, but a negative report would be an almost insurmountable obstacle.

Plans to involve the Academy coalesced soon after the Cold Spring Harbor meeting in June 1986. On July 3, John Burris, executive director of the Board on Basic Biology at the Academy, wrote a short proposal to fund a small group meeting to discuss the genome project as an add-on to an August 5 meeting in Woods Hole, Massachusetts.[4] This was a new addition to the agenda, not anticipated at the March 3 meeting of the board.[5] The project was quickly approved, and on July 10, Burris sent out a tentative agenda and background materials, including clips from the *New York Times* and a summary of the DOE meeting in Santa Fe.[6–9]

Francisco Ayala of the University of California, Irvine, chaired the August 5 afternoon session. David Smith was there for Charles DeLisi, who declined an invitation to go himself. Ruth Kirschstein, director of the National Institute of General Medical Sciences, represented NIH. The group included a high concentration of powerful figures in science.[10] The board noted its support for physical mapping and expressly withheld its support from a massive sequencing program. The board met again the morning of August 6 and agreed that there should be a series of technical workshops and that the NRC staff should develop a proposal for a study. The Commission on Life Sciences, parent body to the board, met the next day and also encouraged development of an NRC

study. Meeting minutes suggested that "the project should be designed primarily to look at mapping of the genome, with consideration given to the international cooperation in this effort."[11] A study proposal was written and approved by the Academy's governing board on September 23, as proposed by the Commission on Life Sciences and the Board on Basic Biology.[12] At Watson's suggestion, Burris forwarded the proposal to Michael Witunski of the James S. McDonnell Foundation. The McDonnell Foundation responded



Bruce Alberts chaired the National Academy of Sciences / National Research Council committee that crafted the scientific strategy for the Human Genome Project. Alberts, who was then a professor of biochemistry at the University of California at San Francisco, is now president of the NAS. *Courtesy National Academy of Sciences*

positively to the proposal and had a check to the Academy to fund the study in less than a month.[13]

The NRC appointed Bruce Alberts chairman. Alberts, a molecular biologist at the University of California at San Francisco, was a brilliant choice. He had written an editorial in *Cell* the previous year that argued against Big Science in biology.[14] He had taken no position on the genome project, but would be seen as neutral or inclined to oppose it. Furthermore, his experience in writing a major textbook *(Molecular Biology of the Cell)* confirmed his talents in managing large writing projects. The original hope was to complete the NRC study in six months, or at least by midsummer 1987.

Several others identified as skeptics were appointed to the panel, notably Botstein and Shirley Tilghman. The committee was peppered with Nobel laureates, including Gilbert, Watson, and Nathans. Sydney Brenner was invited to represent the views of British mappers and sequencers, and John Tooze from the European Molecular Biology Organization in Heidelberg was a second well-connected European. Russell Doolittle from the University of California at San Diego was a pioneer in analyzing data about protein sequences and managing databases. Charles Cantor was a physical mapper, Hood was the expert in instrumentation, and Ruddle was a major force in somatic cell genetics and databases for gene mapping. McKusick, Leon Rosenberg (dean of Yale Medical School), and Stuart Orkin (whose Harvard Medical School laboratory had done seminal work on chronic granulomatous disease and several other diseases) represented human genetics.

Alberts and Burris hatched a strategy intended to slowly build consensus, if that proved possible. The first meeting on December 5, 1986, was intended to give the committee a general sense of the lay of the land, with presentations from the U.S. organizations with special genome-related activities—NIH, DOE, the National Science Foundation, HHMI, and the congressional Office of Technology Assessment (OTA). A survey of activities in Europe followed. The remainder of the day was devoted to what the report should cover and what further information the committee needed to make policy recommendations.

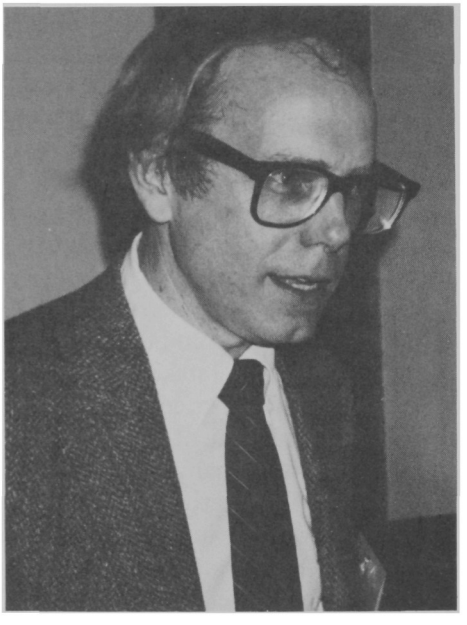
Burris and Alberts elected to focus early meetings almost exclusively on technical background and to postpone discussion of policy options and funding until the technical stakes were clear. The committee opted to bring in those with "hands-on" experience in the technologies under discussion, prudently divining that subsequent policy debates would be less acrimonious as the facts themselves settled many points. At a January 19, 1987, meeting, Maynard Olson from Washington University and others discussed physical mapping, genetic linkage mapping, and somatic-cell genetics.[15] Scientists running major sequencing projects were asked to ground the sequencing discussion in technical realities.[16] Several investigators with direct experience in mathematics, computation, and database management covered informatics and mathematical analysis. Alberts became convinced that he needed someone like Olson, a person deeply involved in actually doing the molecular biology, to balance more senior technological optimists on the committee.[17] After that meeting, the dynamics of the committee took an interesting turn.

In February 1987, Walter Gilbert announced plans to form the Genome Corporation, to map and sequence the genome in a private company. He resigned from the NRC committee to avoid a conflict of interest. Gilbert had consistently proselytized for a fast-track genome project and had always been optimistic to the extreme in projecting timetables and budgets. He despaired of the government ever acting decisively to mount a genome program. Several committee members felt Gilbert was such a strong champion that he impeded

consensus; his assertiveness provoked a backlash. His resignation paradoxically made it possible for those skeptical of the project to participate in redefining it.

Helen Donis-Keller, James Gusella, and Ray White, the leading figures of genetic linkage mapping, opened the next NRC committee meeting in March 1987. The afternoon was a snapshot of the political landscape, with presentations from OTA and Wyngaarden about prospects for securing funds from Congress and a discussion of NIH-DOE politics.

Maynard Olson was appointed to the committee just before Gilbert resigned. Alberts later called the addition of Olson his "major contribution to the NRC committee."[18] Olson's work in physical mapping and large DNA fragment cloning was at the heart of the science under discussion, and he



Maynard Olson served with Alberts on the NRC committee on the Human Genome Project. A specialist on the physical mapping of yeast chromosomes, Olson and his colleagues at Washington University in St. Louis developed the yeast artificial chromosome, or YAC, which made it possible for very long DNA sequences to be replicated. He is now at the University of Washington in Seattle. *Courtesy Victor McKusick*

brought quiet but occasionally biting insights to the discussion. Because he had direct experience with the methods, he could argue convincingly that the seductive theoretical schemes glibly promulgated in the press and on the committee were unlikely to work as advertised.[17] Moreover, Olson's philosophical approach and dry humor were well suited to illuminate conceptual muddles and to forge consensus on a technical base.

It was Olson who noted the importance of having sufficient genetic linkage markers to help orient a physical map, thus cementing the union of genetic linkage and physical mapping. Olson also concisely articulated what might distinguish genome research from other genetics. Olson's guiding philosophy was an extension of Frederick Sanger's tradition at the MRC laboratory in

Cambridge, England—to illuminate function by analyzing structure in projects of increasing scale. (By fostering projects regarded as just barely possible, the boundaries of technique could be extended, and used to elucidate biological function.) Olson argued that projects should be considered genome research only if they promised to increase scale factors by threefold to tenfold (size of DNA region to be handled or mapped, degree of map resolution, speed, cost, accuracy, or other factors.) By the end of the March meeting, it was clear that the skeptics had been converted by redefinition of the genome project's goals.

The consensus emerged most clearly in a discussion of budget recommendations. A subgroup was delegated the task of producing budget options. Botstein spearheaded this effort, and presented three options: $50 million, $100 million, and $200 million, with completion dates sooner for the higher figures (the year 2000 for $200 million versus 2025 for $50 million). The estimates were based on technical presentations at previous meetings, but were adjusted to reflect how many people in how many laboratories could be funded at the different budget levels. Watson objected to the process, noting that it would naturally incline the committee members to seem reasonable by choosing the middle option. He therefore suggested an option of $500 million per year. Since Botstein had already dubbed the $200 million annual budget the "crash program," Watson's became the "crash crash." Comments started from Botstein's right and went counterclockwise around the table.

One by one, members supported a dedicated genome effort, although there was no discussion of which budget figure to choose until a second round. Having demonstrated unanimous acceptance of the importance of a genome program, the committee in the second round achieved general acceptance of something near the $200 million figure. Botstein was made responsible for reviewing the figures again after the discussion. The committee ultimately projected a need for $200 million a year for fifteen years: $60 million for ten centers, $60 million for grants and technology development, $55 million per year in early years for construction and capital costs, and $25 million per year for administration, quality control, and review.[19]

While the NRC process was in midstride, the Council of the American Society for Biochemistry and Molecular Biology issued a policy statement on the genome project. Bruce Alberts was also involved in this effort, which recommended physical and genetic linkage mapping. The council sharply condemned a genome project of the type promoted by Gilbert and was also clearly concerned the project might involve only a few national laboratories under the thumb of DOE. The statement concluded:

> A large-scale, massive effort to ascertain the sequence of the entire genome cannot be adequately justified at the present time. . . . The Council wants to state in the clearest possible terms our opposition to any current proposal that envisions the establishment of one or a few large centers that are designed to map and / or sequence the human genome. . . . It is of the utmost important that traditions of peer-reviewed research, of

the sort currently funded by the National Institutes of Health, not be adversely affected by efforts to map or sequence the human genome.[20]

The statement was intended to thwart a DOE end run that might carry off the genome project, and also to cut short a Gilbert-style monolithic project. Genome politics by now engaged the entire biological community, the national laboratories, NIH, and DOE. The NRC committee was a microcosm of these politics. Its deliberations for the first time systematically assessed the arguments for and against a dedicated genome project, among a panel deliberately selected for balance. Producing a full-length report, through the standard NRC process, required the committee to justify its recommendations at some length.

The NRC committee surveyed the various technical components necessary to produce a coherent genome project and merged them into a scientific strategy. Alberts called the NRC committee "the most fun of any committee that I have worked on" because of "the talented people on it, the rapid learning process it entailed, the uncertainty of its outcome, and its direct impact on policy."[21] The NRC report succeeded to a remarkable degree in setting scientific agenda. This was the critical missing element from 1986 to early 1988. The NRC committee experience changed the course of Alberts's own career, as he subsequently became chair of the Academy's Commission on Life Sciences, and in July 1993, president of the entire NAS.

The NRC report stated that "acquiring a map, a sequence, and an increased understanding of the human genome merits a special effort that should be organized and funded specifically for this purpose."[19] It then outlined goals for genetic linkage mapping and physical mapping. Regarding the vexing question of sequencing, the committee said that "the ultimate goal would be to obtain the complete nucleotide sequence of the human genome, starting from the materials in the ordered DNA clone collection. Attaining this goal would require major (but achievable) advances in DNA handling and sequencing technologies."[19] Olson's scaling idea became a major bullet. Toward this end, the committee recommended pilot sequencing projects and a program to improve sequencing technology. Research on animals and selected lower organisms was marked as essential to make the human maps intelligible.

Agencies were urged to start first with a peer-reviewed grant program and progress toward larger and more targeted projects only as technologies matured. The direct impact of the NRC committee was seen in the March 1988 hearings for NIH's 1989 budget, when Representative William Natcher, chairman of the House appropriations subcommittee that funded NIH, referred directly to the report. It had been released several weeks earlier, and Natcher referred specifically to its budget projections.[33]

The Academy report had one critical weakness—its recommendations about how the project should be organized. The scientists on the committee made little attempt to survey what the agencies were doing in any detail. Their

interest and experience were not in science administration in the federal government, but in science. Yet NIH, DOE, and Congress were percolating ideas about genome projects vigorously. The NRC committee members had informal contacts, principally with NIH, but there was no systematic attempt to gather information about the bureaucratic elements. The federal bureaucracies were highly complex, and the political process of their interactions with one another and with Congress was unpredictable. Having an impact on policy required knowledge about the workings of large bureaucracies, jurisdictional boundaries in Congress, and the histories of pivotal figures making decisions. One former science agency director was sent the penultimate draft of the NRC report as a reviewer. He was "appalled" by the organizational options and conveyed his dismay to the committee and NRC staff, provoking a rewrite of the section on administration.[22] Other reviewers had similar, although less pointed, concerns about the organizational options. Subsequent interviews with committee members indicated that the committee did not have enough data on which to base a recommendation, but felt it had to do so to execute its responsibility.[23] There had not been a meeting to discuss project organization and administration, and last-minute phone calls did not crystallize a solid consensus.

The report was released recommending that there be one lead agency, but "in a move that may leave those in Congress scratching their heads, the committee declines to specify whether it should be NIH or DOE."[24] The report failed to address what would happen if Congress tried to choose between the agencies. If plans had been drawn from scratch, the NRC's recommendation would clearly have been the preferable organizational structure. By early 1988, however, each agency had a multimillion-dollar budget, advisory committees, planning documents, and just as important, expectant constituencies and congressional patrons. If the committee intended that one agency should have a formal mandate to complete the genome project, with funding coming from several pots, then it would have been politically feasible, but ineffective. How could NIH decide how DOE should spend its funds, or vice versa? If a lead agency controlled all the funding from one pot, then either the NIH or the DOE program would have to be dismantled. Creating a program was considerably easier than burying one; the NRC recommendation proposed a politically hopeless task and invited open warfare between NIH and DOE, a war that might well kill the very project NRC intended to promote. In the end, Congress ignored the organizational recommendation and correctly read the bottom line of the NRC report to be a powerful endorsement of the genome project's scientific content.

The report was released to great fanfare on February 11, 1988, in time to be discussed at an annual meeting of the American Association for the Advancement of Science later that week. *Science* covered the release, noting that "the committee, like much of the biological community, was divided . . . when it began, but after a year of deliberation, it came out resoundingly in favor of

the project."[24] Other scientific journals and daily newspapers reported on the Academy's approval of "the genome project"; many of the headlines featured the budget recommendation.[25–32] The NRC conception of the genome project promptly displaced the original proposals focused on sequencing. NIH, with some backroom politicking by committee members, took the NRC report as an invitation to active participation.

James Wyngaarden, director of NIH, used the NRC report as the organizing focus for an *ad hoc* planning meeting held two weeks after the NRC report was released. This organizational meeting involved many NRC committee members and set the agenda for the growing NIH commitment. The course charted by the NRC committee gave Wyngaarden enough rudder to break the inertia of an unwieldy NIH ocean liner, and to steer it in a new direction.

11

The NIH Steps Forward

JAMES WYNGAARDEN played the central role in securing NIH's genome budget. President Reagan nominated him to become NIH director in spring 1982. Wyngaarden came from Duke University, where he was chairman of the department of medicine for fifteen years. He was highly respected as a clinician and human geneticist. He accepted the job with some reluctance, and said so openly in confirmation hearings before the Senate: "I did not actively seek the post. . . . my acceptance of that honor is out of a sense of obligation based on an awareness of the vital role of NIH in biomedical research."[1] He accepted the position because of considerable worry about what might happen to NIH if a caretaker was nominated instead of a person thoroughly familiar with biomedical research.[2]

NIH's preeminent role in biomedical research drew on its hundred-year history. NIH began with $300 in laboratory equipment in an attic of the Marine Hospital on Staten Island, New York. Joseph Kinyoun, who directed the small Staten Island laboratory, had been trained by one of the most prominent bacteriologists of the day, Robert Koch. The laboratory was rescued by Surgeon General John Hamiliton from a congressional assault in 1888, and Kinyoun remained its director until 1899. It moved to Capitol Hill in Washington, D.C., as the Hygienic Laboratory in 1891. Senator Joseph Ransdell introduced a bill to increase appropriations for the Hygienic Laboratory and to create a separate National Institute of Health in 1926. When he combined the two organizations into one, he won passage in 1930. The Hygienic Laboratory was thus transformed into the National Institute of Health. The Wilson family of Bethesda, M.D., donated part of their estate to the government in the 1930s, and construction of facilities began in October 1938.

Biomedical research flourished in large part because of increasing federal funds. The national institute became plural with the establishment of the National Cancer Institute in 1937.[3] The NCI was made a part of the NIH when President Franklin D. Roosevelt signed the Public Health Service Act of 1944 (Public Law 78-410).[4] NIH moved to Bethesda in 1940. During the war, biomedical research joined many other parts of science in the war effort.

The Office of Scientific Research and Development guided science policy

during the war. Much of the biomedical research effort focused on keeping soldiers healthy; researchers studied venereal diseases, yellow fever and malaria, and mental health. As the war neared an end, polio, cancer, and motor-vehicle accidents emerged as major health problems. As the wartime Office of Scientific Research and Development closed down its efforts, it transferred many programs to existing agencies. The set of contracts for biomedical research was quietly turned over to the National Institutes of Health, with no public notice.[5] This thwarted a more centralized approach to science that would have placed all research under a single agency. Vannevar Bush, principal architect of the plan to sustain science after World War II, favored a single science foundation that would encompass biomedical research as well as all other fields. Senator Claude Pepper, chairman of the Senate Committee on Health and Education, and several others favored a separate biomedical research organization. Pepper and his congressional colleagues held sway. The NIH emerged as the dominant funder for biomedical research during the several-year post-war delay in creating the National Science Foundation.

NIH's emergence from the shadows was not a carefully orchestrated strategy. Rather, NIH took shape through diligence and serendipity. In 1945, Cassius J. Van Slyke had a heart attack. He was running a venereal disease service for the Public Health Service, and his friends wanted to find something less strenuous for him to do. Ernest Allen had joined him in 1943, amid the war effort, at a facility in Augusta, Georgia. Allen was invited to administer sixty-six federal contracts slated to terminate on June 30, 1946, an "incidental, part-time, lower-left-hand-drawer-of-the-desk sort of activity."[4] Congress appropriated $8 million for 1947, of which $4 million was for extramural grants. A big part of the budget was for antibiotics. When the cost of making penicillin dropped precipitously, existing contracts could be smaller, thus freeing up funds for other purposes. Van Slyke and Allen cast about for ideas about what to do with the residual funds.

Van Slyke and Allen innocently sent a letter to medical school deans: "We have limited funds available for research purposes. If you have investigators who need these funds, let us know by return mail." They provoked a landslide. Allen later called the missive "the most naive letter ever to emanate from the national government in Washington."[4;6] Within a year, they received more than a thousand responses. Between January 1946 (when the OSRD contracts were transferred to NIH) and the end of August 1947, NIH doled out $10 million to nongovernment institutions.[4] Even so, there were more proposals for research than funds to support them, and NIH sought an increased research budget the next year, the first of what would thereafter become an annual ritual. Thus began the largest extramural grants program in the world. So much for Dr. Van Slyke's part-time job.

NIH grew explosively and with aggressive lobbying efforts expanded its mandate and funding. The pivotal event was a coalition of media supporters,

advertising executives, members of Congress, White House contacts, and a lobbyist hired specifically to bolster biomedical research funding.[7;8] Mary Lasker and Florence Mahoney were leaders in the outside effort, working closely with Senator Pepper and other members of Congress. These champions convinced Congress to view biomedical research as a public investment and focused on diseases of high prevalence and severity, particularly cancer, heart disease, and mental illness. Biomedical science administrators were at first reluctant to expand their vision so grandly, and leaders of science (including the president of the National Academy of Sciences) were suspicious of a larger federal presence. The prospect of a biomedical research establishment outside their control, however, induced leaders of the Public Health Service, including the NIH, to join in the battle. The expansion of NIH's mission and money attracted a second generation of able administrators with great vision.

James Shannon, who became NIH director in 1955, regarded his first few years as critical. The NIH budget tripled from $98 million in 1956 to $294 million in 1959.[5] Before he became director, Shannon developed close working relationships over the years with Representative John Fogarty and Senator Lister Hill, chairmen of the appropriations subcommittees with jurisdiction over NIH. Shannon also cultivated relationships with their staff directors. When he became NIH director, he chose his political strategy. "I was less concerned with the budget per se than the development of a conceptual base for the mission of NIH in broad terms. . . . My salable item was opportunity, not need. . . . We did not ask for specific things in terms of specific budget increases we would like. Rather, we discussed long-range goals and the strategy we would use in their attainment, given adequate funding."[5] This powerful triumvirate of Fogarty, Shannon, and Hill fell apart in the late 1960s. Fogarty died in January 1967, Shannon left the NIH directorship in 1968, and Hill retired from the Senate six months later.[5]

Shannon was the first of many NIH directors to find himself in a delicate position, with divided loyalties between his superiors in the executive branch and Congress. Executive branch administrators generally looked at NIH budget increases with some alarm, while congressional patrons consistently fostered them. Part of the tension grew from the bureaucratic locus in which NIH found itself. The NIH director represented but one of several agencies within the Department of Health, Education, and Welfare (later, Health and Human Services). The director sat several layers down in the bureaucracy. Shannon's budget expansion was so fast that it made Health Secretary Marion Folsom uncomfortable. Folsom sought outside advice, but the committee he appointed endorsed Shannon's strategy.[5]

The expansion of NIH got a major boost when the War on Cancer became a presidential issue. Mary Lasker and a legion of biomedical research advocates, grown sophisticated over a decade and a half of experience, were key forces behind the initiative. In his January 1971 State of the Union speech, President Nixon announced:

The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease [cancer]. Let us make a total national commitment to achieve this goal.[9]

After a circuitous political route, the President signed the National Cancer Act on December 23, 1971.[9] Congressional largess also extended to the rest of biomedical research. As the NIH grew for several decades, the NIH budget, while remaining a very small part of the total disbursements of the department, accounted for a larger fraction of "discretionary" funds.[10] Most of the funds in the department went to entitlement programs—Social Security, Medicare, and Medicaid—over which administrators had relatively little control. NIH programs, in contrast, were subject to annual appropriations, more subject to administrative control. Congress, however, treated NIH with special care. The NIH director often found it easier to find support for NIH programs in Congress than among his superiors in government.

The NIH director thus walked a tightrope between serving his bosses under the President, answering to a rambunctious constituency of biomedical researchers almost monomaniacally obsessed with more research funds, needing to establish research priorities to respond to a changing world, and attending to the wishes of congressional patrons. Congressional support was often the most reliable element, but entailed its own difficulties as individual representatives and senators desired specific programs from NIH.

The job of NIH director could be awkward. Bernadine Healy wrote about the NIH three years before becoming the first woman to direct it:

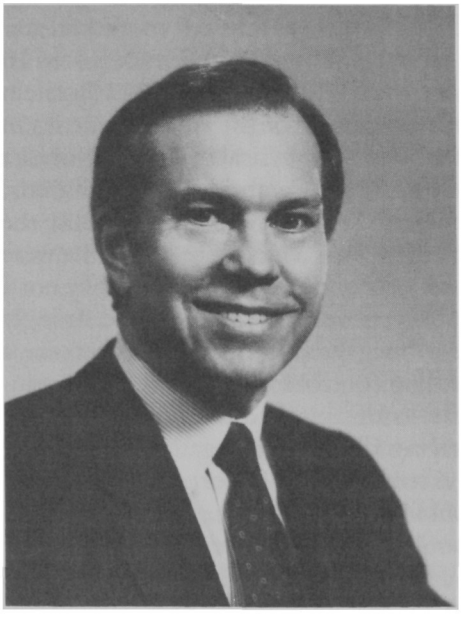
The NIH is a jewel—loved by all, especially Congress. But the budget process, by precedent and design, keeps the NIH under constant scrutiny, subject to much micromanagement. . . . NIH is subject to staggering political manipulations, disease- and constituent-directed earmarking, and intense programmatic review—more extensive than that experienced by virtually any of the other research and development agencies. The pressure is from both the Congress and the Office of Management and Budget . . . [but] the bureaucratic infrastructure keeps NIH and institute directors sufficiently low on the totem pole that they do not have the ready political access their exposure and scrutiny would suggest they deserve.[11]

NIH was a remarkable institutional innovation of the postwar era, the preeminent biomedical research organization in the world. It was nonetheless amazing that it ever got anything done.

NIH remained the largest single funding source for biomedical research until 1982, when private industry, led by the pharmaceutical industry, exceeded NIH's contribution.[12] This was the same year that Wyngaarden became director. Robert Marston, who directed NIH from 1968 to 1973, believed that the tacit understanding of NIH in the upper reaches of the executive branch dissolved during the 1980s, replaced by fiscal and political concerns.[13] This was the climate that prevailed as James Wyngaarden contemplated the human genome.

Wyngaarden first focused attention on the genome project in mid-1985. Robert Sinsheimer spoke to him about the first ideas for a Santa Cruz sequencing institute in March 1985, but Wyngaarden barely remembered this meeting several years later.[2;14] Wyngaarden was present when Renato Dulbecco unveiled his idea for genome sequencing at the Italian embassy in mid-1985, but Dulbecco remembered this, not Wyngaarden.[2] The idea hit home only when Wyngaarden heard about DOE genome plans in London, at a meeting of the European Medical Research Council, June 4–7, 1986. Someone, he does not recall who, asked him what he thought about a DOE plan to spend $3.5 billion on sequencing the genome. He was shocked; the idea seemed to him "like the National Bureau of Standards proposing to build the B-2 bomber."[2] At roughly the same time, Ruth Kirschstein, director of the National Institute of General Medical Sciences (the main patron of basic genetics among the NIH institutes), began to get feedback from DOE's March 1986 workshop in Santa Fe.

Charles DeLisi had invited an NIH representative to the Santa Fe meeting,



James Wyngaarden, as director of the NIH from 1982 to 1989, was responsible for securing the first NIH budget for human genome research. The NIH quickly overcame the DOE headstart to become the lead agency for the U.S. genome effort. *Courtesy National Institutes of Health*

but the invitation got lost in the deluge of mail that pours into the NIH director's office. DeLisi sent materials about the meeting afterward, as preparation for a meeting with Wyngaarden and Norman Anderson, but this got little attention until Wyngaarden returned from London. Upon his return from London, Wyngaarden asked Kirschstein to convene a group to decide how NIH should respond to DOE's overture. Kirschstein summarized the

June 27 meeting of that group in a memo to Wyngaarden, noting that "first and foremost, while it is clear that the Department of Energy has taken, and will continue to have, the lead role in this endeavor, the NIH must and should play an important part."[15] The bottom line was profound ambivalence, the tale of pushmi-pullyu translated into NIH argot.

The NIH group recommended that Wyngaarden focus the October Director's Advisory Committee meeting on the genome project because "the debate started at Cold Spring Harbor and reported in the *Science* article should be extended in order to determine how the international scientific community truly views this project."[15] Between October and the end of the year, NIH could incorporate any recommendations into the fiscal year 1988 budget. They also noted the need for increased support of GenBank, the database funded by NIGMS to archive and disseminate DNA sequence information.[15] Kirschstein wrote to DeLisi—and Wyngaarden to DeLisi's boss Alvin Trivelpiece, establishing the bureaucratic pecking order—agreeing that the NIH and DOE should talk at the July informational forum organized by the Howard Hughes Medical Institute (HHMI).[16;17]

The October 16–17, 1986, meeting of the NIH Director's Advisory Committee followed on the heels of the HHMI forum and featured another all-star cast. The aura of Nobel laureates and aspirants suffused Conference Room 10 in Building 31, the same site used for the HHMI forum. David Botstein opened the technical discussion with an overview of the role of genetics in understanding biology. Charles Cantor reviewed physical mapping. Nobelist David Baltimore, from the Whitehead Institute in Cambridge, Massachusetts, spoke to the science policy issues. He asserted that a proposal to sequence the genome would be useful, but would merit at best a mediocre score if he were voting in a scientific review group. Lack of sequence data was generally not a limiting feature, although lack of a global genetic map was. He urged strongly that the genome project not become a "megaproject" that would become a political creature of its own right, handing control from scientists to bureaucrats and politicians. He echoed these sentiments in a subsequent article.[18] Dulbecco challenged Baltimore by saying that the aggregate cost of doing many small projects would drastically exceed the cost of an organized program. Botstein countered that the costs would be higher, but the amount of information beyond mere sequence data would also be significantly greater.[19;20]

The meeting then systematically surveyed NIH, DOE, HHMI, and NRC genome efforts, and then, briefly and incompletely, efforts in Japan and Europe. Allan Maxam presented a group of guiding principles that would make the program most useful. It should be (1) promoted as the Human Genome Project, and have human genetics as its ultimate goal; (2) designed to include comparative genetics with other organisms; (3) linked to protein and RNA catalogs and research efforts; (4) made relevant to related fields such as anthropology, paleontology, and evolutionary biology; and (5) planned so that new databases were compatible with existing genetics databases and others in re-

lated fields. Russell Doolittle noted that if the purpose was mapping, then databases were essential, analogous to the star map or the coastal surveys conducted with federal funds. Yet existing databases were already collapsing under the weight of new data. GenBank, for example, was behind in data entry and was precluded from developing algorithms and software under its NIH contract. Donald Lindberg, director of the National Library of Medicine (NLM), spoke about the manageable magnitude of the database task, but also the need to dedicate resources to it. Ronald Davis, from Stanford, reviewed work in yeast that presaged the yeast artificial chromosome technique that enabled cloning of megabases of DNA, and Charles Cantor from Columbia University, in his second talk of the day, reviewed techniques for analyzing such large DNA fragments.

The format was more structured than that of the HHMI forum three months before, and the policy issues were more salient. The main conclusions were that (1) NIH should eschew Big Science or a crash program, (2) the study of nonhuman organisms was important to make map and sequence data useful, (3) it was too soon to start sequencing, but pilot projects might make sense, and (4) information-handling was already a problem.[20] *Nature* observed, "The initial polarization of opinions has given way to a more constructive consensus that some concerted effort can begin without rending the fabric of biological science."[21]

An NIH Working Group was appointed after this meeting. Wyngaarden chaired the working group, which also included the directors of several NIH institutes, centers, and divisions: Kirschstein, Duane Alexander (director of the National Institute of Child Health and Human Development), Betty Pickett (director of the Division of Research Resources), Lindberg (NLM), and Jay Moskowitz (Program Planning and Evaluation). George Palade (Nobel laureate from Yale) was the lone outsider. Rachel Levinson was named executive secretary of the working group, the staff person most closely tracking genome activities. The group met on November 6 and December 16. The November meeting focused on improving communication among the managers of various NIH-supported databases and information resources, to be followed by linkage to non-NIH American ones and finally international nodes.[22]

In early December, Wyngaarden briefed staff from several House legislative committees and from OTA about NIH genome activities, and Senate staff requested a similar briefing. At the December 16 meeting at NIH, Wyngaarden indicated that he wanted to signal Congress that NIH's support of genome research should be channeled through routine grant mechanisms. The working group agreed to work toward program announcements over the next few months.[23] These were indications of interest from NIH, but did not carry set-aside funds or entail special review procedures. The program announcements were published May 29, 1987.[24;25]

The NIH Working Group also discussed how to respond to an OTA request for information about what NIH was already doing in the way of

genomic research. At a December 4 meeting with Kirschstein and Levinson, Patricia Hoben and I (on behalf of OTA) explained our need to gather information about NIH activities for Congress. Kirschstein saw no easy way to answer our questions, because the categories of interest did not fit those used to sort grant applications. There was no way to pull out computer records by a simple search. The NIH Working Group decided to make some uniform definitions and ask the various institutes, bureaus, and divisions of NIH to cull through their portfolios.[23] This proved an elaborate and time-consuming task, and ultimately proved a politically divisive exercise.

Wyngaarden's early concern was to ensure that NIH had a major role in any large genome program, but he did not want to make any premature long-term commitments. He was in favor of the concept of the genome project "from the very start," but did not want to get too far in front of his biomedical research constituency when there was so much dissension among them. He likened his position on the genome project to Lincoln's waiting for success at Antietam before announcing the Emancipation Proclamation, so as not to jeopardize Union support in Europe. His second analogy was Roosevelt's delay in pushing the pre–World War II Lend-Lease Act until public sentiment supported the course he had already chosen.

Wyngaarden did support the genome project where it counted the most—in the appropriations process. This was a process he had come to understand well. The NIH had an unusually complex and protracted budget process. Each individual institute, division, or center submitted a budget request two years in advance. This was integrated in the NIH director's office into a set of budget requests, although technically there were eighteen separate budgets. The NIH aggregate requests went to the assistant secretary for health, responsible for all Public Health Service (PHS) agencies, including NIH. This budget went then to the department secretary's office and was made to fit with other arms of the department. Finally, the departmental budget was forwarded to the Office of Management and Budget, and then to the President.[26] Each institute's budget, therefore, had six levels of negotiation before it was presented to Congress (1, institute; 2, NIH director; 3, PHS; 4, department; 5, OMB; 6, President).

Article 1 of the U.S. Constitution gave Congress sole authority to tax and spend for the federal government. The President's budget request, from the congressional perspective, was merely the first step in the real budget process. Within Congress, the budget was handled first by an appropriations subcommittee and then a full committee in the House, passed by the full House, and then forwarded for action by the subcommittee and committee in the Senate. The subcommittee chairmen, ranking minority members, other subcommittee members in both houses, and staff (not necessarily in that order) all had power over the NIH budget. Wyngaarden, like all other NIH directors, had to master this process, with its immense parliamentary complexity and ample opportunity for blundering into some appendage attached to one of the players. Wyn-

gaarden took his handling of the budget as a point of pride. He opened an article on the centennial of NIH by stating that "the most satisfying aspect of my first five years as director of the NIH has been the sustained growth of NIH funding."[26] Wyngaarden knew that most NIH policy was determined by the appropriations process, and regarding the genome project, he focused on this objective.

In his summary statement to the House and Senate appropriation committees for fiscal year 1988 (in February and March 1987), he cast gene mapping in high profile. The description of the extra dollars requested for gene mapping did not match the scientific strategy then being outlined by the NRC committee, hinting only at extensions of ongoing gene hunts, but it was still a new line item in the NIH budget. In his statement, Wyngaarden mentioned NIH's centennial, the urgency of AIDS research, and then the genome project. A straight reading of his text suggested gene mapping was second in priority only to AIDS.[27]

The NIH appropriation for genome research did not require a special authorization, as it clearly fell within the bounds of NIH's biomedical research mission. Unless someone in Congress objected, much could be done through appropriations alone. Fiscal year 1988 was one of the years when the NIH budget dance ignored the beat of the administration request, as Congressman David Obey made explicit in his comments. Because the NIH director was part of the administration, however, Wyngaarden had to toe the administration line, defending the official administration requests before Congress. Testimony before legislative or appropriations committees was reviewed by officials in the Department of Health and Human Services and in the Office of Management and Budget. The ponderous bureaucracies had notoriously thin skins and brooked little deviation from settled policy; in the absence of an explicit policy directive from above, new initiatives were viewed with skepticism.

Wyngaarden noted the delicate balancing act by quoting an order from Harry S. Truman to his agency chiefs, directing them not to request more funds from Congress than he as President requested. Congress had leeway, however, to ask "factual questions" to which agency heads could respond.[26] The bureaucracy could not interfere with Congress's authority to ask whatever questions it liked, and interfering with honest answers was a violation of federal whistleblowing laws. Over the years, appropriations committees had devised hypothetical questions as a way to tease apart NIH's true priorities from administration malarkey. Each year, they asked the NIH director what he would do with sums of money in addition to those requested, in $100 million increments.

In his replies to the House Appropriations Committee for fiscal year 1988, Wyngaarden asked for $30 million in genome research funds as part of the fifth $100 million increment, and another $15 million in the eleventh increment (of twelve).[27] Michael Stephens, on the staff of the House Appropriations Committee, recalled making some minor modifications in the final NIH

budget, adding a few special projects, and stopping somewhere between increments five and ten in NIH budget additions that year.[28] The starting point, however, was Wyngaarden's blueprint, based on his personal judgment, input from the Director's Advisory Committee, and the NIH genome Working Group.

After Wyngaarden testified in early spring 1987, Nobelists David Baltimore and James Watson briefed members and staff of the House and Senate appropriations committees. They were invited to speak informally as part of a series of meetings occasionally arranged by Bradie Metheny of the Delegation for Basic Biomedical Research (affectionately known around NIH as the Nobel Delegation). Baltimore and Watson met briefly before the session on May 1 to go over their remarks. The meeting included Congressmen William Natcher and Silvio Conte, chairman and ranking Republican of the NIH appropriations subcommittee, and also Rep. Joseph Early, a subcommittee member and staunch NIH supporter of many years. Senator Lowell Weicker, who had been chairman of the Senate appropriations subcommittee for NIH until late 1986, was also present.[29–31] Just as important, the senior staff from the appropriations subcommittees of both houses were present. The principal aim of the meeting was to promote funding for AIDS research, but Watson availed himself of the opportunity to seek another $30 million for genome research.[32]

The House responded to Wyngaarden by appropriating $30 million for genome research, the amount in the fifth increment and the same as the amount requested by Watson. The Senate was less enthusiastic. Maureen Byrnes, staff to Senator Weicker, recalled that he was not as enthusiastic about the genome project as the House delegation; other senators, such as Tom Harkin, were more enthusiastic but less senior, and did not get to set the mark.[33] Michael Hall, staff director for the new chairman of the Senate subcommittee, Lawton Chiles, got no clear signal of strong support and put $6 million in the Senate bill. The House and Senate bills went to a conference committee for resolution of differences. The arithmetic mean of $18 million emerged from the House-Senate conference. The bill passed and became law. A Gramm-Rudman-Hollings recision reduced the final appropriation to $17.2 million for genome research at NIGMS that year. In private conversations, NIGMS staff estimated that $5 million of this was diverted from existing programs and the rest was "new" money.[34;35]

An additional $3.85 million funded a new National Center for Biotechnology Information at the National Library of Medicine (NLM). The NLM regents, principal overseers of the library, identified molecular biology as an important area. An outside support organization, the Friends of the National Library of Medicine, took up the cause. The result was a bill, largely drafted by NLM and the Friends of NLM, prepared for Congressman Claude Pepper, the same man who as a senator more than three decades earlier had been instrumental in establishing NIH as the dominant biomedical research agency.

The NLM bill was to establish an information management center to

support the biomedical research and biotechnology efforts in the United States. It added a new NLM budget authorization rising to $10 million annually. Pepper held a moving hearing on the bill on March 6, 1987, at which the victims of genetic diseases testified. Victor McKusick recounted his positive experiences working with NLM to computerize *Mendelian Inheritance in Man* and underscored the urgency of managing the explosion of information about human genetics. Other prominent scientists, NLM director Donald Lindberg, and HHMI President Donald Fredrickson also voiced their support.

The bill got caught in legislative complexities, however. The hearing was held in Pepper's subcommittee of the Select Committee on Aging, which had no legislative authority. Lindberg was present when Pepper called Henry Waxman, chairman of the subcommittee with legislative jurisdiction. Pepper indicated his wish to hold the hearing, and Waxman apparently agreed. The news did not reach staff members, who ultimately were delegated authority for action in the full committee, however. They learned of the hearing through OTA and NIH.[36;37] NIH, unlike many other agencies, is authorized for three-year intervals as a rule, and 1987 was not one of the years when such a bill was in Congress. There was thus no logical vehicle to which the NLM bill could be attached, and so it stood alone. The NLM provisions were finally folded into the NIH authorization bill that passed more than a year later. The Appropriations Committee acted before then, however, by appropriating $3.85 million for fiscal year 1988, with the understanding that it was to be spent toward the purposes specified in the languishing Pepper bill. Pepper himself testified in favor of this action by the Appropriations Committee.

NIH appropriations for fiscal year 1989 were more or less routine. NIGMS requested $28 million for genome research. This was the final year of the Reagan administration. Congress and the President had agreed on a two-year budget plan the previous fall, in the wake of the October 17, 1987, stock market crash, and the President's budget request held to this agreement. 1989 was the one year under Reagan when the NIH request was taken seriously by the appropriations committees, and the requested amount was granted. The House appropriations subcommittee again asked Wyngaarden what he would spend with additional funds, and the genome project was listed as a potential beneficiary, but this year the incremental funding game was not the basis for appropriations.

There was one sidelight in the 1989 appropriation hearings, in that the NRC report was newly available.[38] Rep. Natcher led off a series of human genome questions by asking Wyngaarden how the $28 million genome budget request from NIH fit with the $200 million recommended by the NRC committee.[39] This gave Wyngaarden an opening to explain that there would be higher budget requests in future years. Wyngaarden ended his answer to this question by noting that "NIH considers the human genome initiative a *very* high priority."[40]

NIH's appropriations for 1990 involved several complications. NIH sent

its budget request to the department and thence to OMB, with a final request of $62 million. When the President's budget request came back from OMB, it sought $100 million for genome research at NIH. The $62 million was apparently increased to $100 million by divvying up monies freed up by removal of other programs during OMB review.[41] The increase surprised NIH and signaled support for the NIH genome project high in OMB or elsewhere in the White House. Confusion surrounded the process, as this was a time of transition from Reagan to Bush, and it was not clear whether support for genome research was a carryover from the Reagan administration or indicated fresh support to be expected under President Bush. In the end it did not matter, as appropriations subcommittee staff in the House used the initial request level, known from NIH planning documents, as the basis for their deliberations. The 1990 appropriation was $59.5 million after some final adjustments.

During negotiations on the 1990 budget, Wyngaarden discussed the need to create a separate administrative center for the genome project, as the genome budget had become sufficiently large. He got agreement from the House to allocate the 1990 budget request to a new center that the Department of Health and Human Services would create by administrative fiat. The Senate agreed to roughly the same budget figure, but left the funds in NIGMS. In conference, the report followed the House, creating a new budget center—the National Center for Human Genome Research. The center was administratively created by Secretary Louis Sullivan, Jr., in October 1990, a new baby in the NIH family.

The baby had to fight for its patrimony even as it was born. The 1990 NIH genome budget was subject to last-minute negotiations in a Senate looking for ways to fund new initiatives elsewhere in the Department of Health and Human Services. One eleventh-hour Senate proposal, put forward and then withdrawn by Senators Pete Domenici and Ted Kennedy, had a genome budget reduction from $62 million to $50 million. The $12 million from the genome office, along with funds taken from elsewhere in NIH, would go to to programs for the homeless.

This illustrated the twofold vulnerability of the genome project as a new program at NIH. First, activities that showed a rapid growth were highlighted by their percentage budget increases and tracked closely by appropriations staff. Second, NIH's large share of the discretionary budget in the Department of Health and Human Services made its budget attractive as a possible benefactor for new initiatives. NIH's $8 billion budget was a plump fruit to be squeezed for new programs in health and social services. Any new sprout on such a bounteous tree was subject to pruning.

Wyngaarden made his greatest contribution to the genome project by securing its budget. He also established the Office of Human Genome Research to coordinate efforts during 1988 and 1989, and convinced his departmental superiors to create the National Center for Human Genome Research.

This gave the genome project a more permanent home in the NIH bureaucracy, and "center" status assured independence by conferring the power directly to disburse funds. Without special attention from him, it is unlikely NIH would have moved with as much dispatch. Wyngaarden did indeed react to the DOE initiative, rather than generate the idea for a program, but his task was no smaller. In an interview just before he left NIH as director, Wyngaarden noted the decline in autonomy of the NIH director since the 1960s. In particular, he noted the "more and more tortuous process for documents of all sorts through the Department and OMB. . . . It's not unusual now for a new policy document to be a year in transit through those various offices."[42]

A 1984 Institute of Medicine report on the structure of NIH noted an "absence of the trappings of bureaucratic authority; hence the director manages largely on the basis of persuasion, consensus, and knowledge."[43] The genome project showed that the NIH director could exercise considerable authority, but not quickly. The NIH process entailed an elaborate advisory mechanism and a slow consensus-building effort, both within NIH and with its outside constituency of investigators.

From the 1970s through the 1980s, NIH grew into a ponderous bureaucracy, with little control exercised by its director. The NIH budget doubled while Wyngaarden was director. The genome project was established in large part through his direct efforts, and it got disproportionate attention. Wyngaarden characterized his job by paraphrasing Yogi Berra; directing NIH was "90 percent damage control, 50 percent budget, and the rest was fun."[2] The genome project counted as fun.

Wyngaarden left NIH in July 1989, several months into the new administration. He served briefly in the White House Office of Science and Technology Policy and then became foreign secretary for the National Academy of Sciences and the Institute of Medicine. In July 1990, the Council of the Human Genome Organization (HUGO) appointed him director. This made Wyngaarden the central figure in HUGO, the last best hope of smooth international collaboration for the genome project. He held this position into 1992, when HUGO took off in a new direction.

The fiscal year 1988 through 1990 budget decisions in Congress, along with the creation of NIH's National Center for Human Genome Research, set up independent projects in both NIH and DOE. They would continue to be funded by separate appropriations bills. In this sense, Congress had spoken, granting both NIH and DOE their wishes for a genome program. The size of the budgets ($58.5 million at NIH and $26 million at DOE) was an implicit measure of relative power. The way the programs would coordinate the work, however, was far from clear. As the genome programs became established, the major topic of discussion moved from whether NIH and DOE should have genome projects at all to which agency should lead the effort. Congress might be the place where that decision was made as well.

12

Tribes on the Hill

THE HONORABLE GEORGE E. BROWN was the first member of Congress to take note of the Human Genome Project. He noticed an article in the *Washington Post* reporting on the July 1986 HHMI forum[1] and offered his encouragement to build toward a truly international effort.[2] Brown was one of a handful of members interested in science, but he attained a position from which he could take action only five years later, when in early 1991 he assumed chairmanship of the House Science, Space, and Technology Committee. While the genome project was forming, he had to content himself mainly with watching developments.

The organization of Congress is inscrutable to newcomers. J. McIver Weatherford, an anthropologist, spent a year on Capitol Hill as a fellow in the program run by the American Association for the Advancement of Sciences. (This was the same program that first brought me to Washington, as well as Eileen Lee, Lesley Russell, and several others who figure in this story.) He wrote a book analyzing the similarities between Congress and tribal organizations.[3] The book, while somewhat flippant, captures some of the central forces that keep an otherwise chaotic institution from completely disintegrating. Vestiges of tribal organization prevail not only in Congress, but also in executive agencies. The decentralized bureaucracy at the National Institutes of Health was a particularly good example, with the director of each institute, center, or division a chief of his or her domain. The two large tribes on two hills—on Capitol Hill and at the NIH campus at the foot of Pook's Hill in Bethesda—organized into multitudinous clans. The bureaucratic organization of the genome project emerged from a Byzantine process of negotiation and politics.

When appropriation committees funded both NIH and DOE genome programs, the question of how the two programs would coordinate their efforts began to dominate discussion. The pressure mounted as budgets grew from $4.5 million DOE-only in 1987 to almost $30 million (both NIH and DOE) in 1988 and to $46 million in 1989. Management of such a rapidly growing enterprise lagged behind efforts to convince congressional patrons of the value of the science. The coordination question first came up in the appro-

priations process. In the spring 1987 House appropriations hearing for the 1988 budget, Congressman Obey asked several questions about genome research, stimulated by another article in the *Washington Post*.[4] Obey wanted to know why DOE was proposing to lead such a project, to which Wyngaarden replied that DOE had legitimate interests in detecting mutations, but NIH was outspending DOE by a hundred to one in the relevant fields, "and so NIH should . . ." Wyngaarden was about to finish his policy recommendation when Obey interrupted, asking for further clarification of DOE's interest. Wyngaarden later told *Nature* that he thought it was presumptuous of DOE to claim leadership when it was spending less than $10 million a year in the area,[5] but he was not pressed by Obey or others on what NIH should do about it. *Science* opened its "Research News" section with a depiction of interagency squabbling[6] and captured the confused positions of scientists and administrators during this formative period as they jockeyed for position at NIH and DOE.

A year later, Wyngaarden was ready with an answer. In questions about 1989 appropriations, subcommittee chairman Natcher again asked what agency should take the lead. Wyngaarden was unequivocal and direct: "I think NIH is the appropriate agency."[7] This flew in the face of what DOE preferred. It disagreed sharply with the recommendations of eight months earlier, from the advisory panel set up to advise DOE.[8] Each agency, not surprisingly, wanted to manage the genome project itself. Asking DOE and NIH which agency should lead was unlikely to provide a consensus. If the agencies reached agreement between themselves, so much the better, but that did not appear to be happening. The President presided over both agencies, providing a theoretical point of coordination, but because the efforts were in two separate departments, there was no lower authority than the White House where negotiations could take place.

The White House had other matters to attend to, and the genome project, while its coordination did reside in the cabinet for a short while, under the Domestic Policy Council, was ill suited for such a scientific and technical task. The upper reaches of the Reagan administration, even more than most, were almost oblivious to biomedical research. The way was left open for Congress to have a decisive voice in how the project unfolded. Congress had already commissioned a report on the genome project, at its Office of Technology Assessment (OTA), and that report focused heavily on just this question of interagency coordination.

The first interest in an OTA report surfaced in late spring 1986. OTA's Gary Ellis and Kathi Hanna invited Victor McKusick to present arguments for mapping the human genome at an OTA biotechnology meeting just before the Cold Spring Harbor symposium. Bernadine Healy chaired the biotechnology panel, and was intrigued. Others at OTA took notice, although no direct action ensued. When news from the Cold Spring Harbor meeting was reported in *Science* and *Nature,* it attracted the attention of several congres-

sional staff members. Lesley Russell, science assistant to chairman Dingell of the Energy and Commerce Committee, and I (then working at OTA) instigated an OTA assessment of the genome project. Interagency conflict was already apparent at that early date, and it seemed likely that Congress would become involved in more than just appropriations. In a memo, I argued for a "simple and direct" project, which would be easiest with a single requesting committee in each house.[9] The proposal that followed focused on several issues:

> The expertise to perform the sequencing resides in several different executive agencies, primarily DOE and NIH. Funding and coordination would thus be complex. Second, this could be among the first "big science" projects in biology, requiring substantial resources over a sustained period. Third, the technologies to do the sequencing and gene mapping would have significant clinical applications, scientific consequences, and industrial spinoff for biotechnology. Fourth, an international effort to map the human genome would have to contend with conflicts between free exchange of data and technology, on one hand, and proprietary and nationalistic interests, on the other.[10]

By pure happenstance, the OTA and NRC projects were approved within an hour of each other on September 24, 1986. I directed a team of exceptionally capable staff for the OTA project. Patricia Hoben, trained in molecular biology at Yale and fresh from a postdoctoral stint at the University of California, San Francisco, kept abreast of technical developments and wrote scientific background chapters. Jacqueline Courteau had obtained her B.A. in the history of science at Radcliffe and was just completing her master's degree from the science writing program at Johns Hopkins. She focused on databases and repositories and on international genome efforts,[11] ultimately compiling the first systematic data on international efforts.

The scientific consensus laid out by the NRC committee was a necessary precondition for the political decision about whether and to what degree a program should be funded. OTA added little to the scientific rationale, but instead focused on the bureaucratic structures and processes. The NRC and OTA reports thus complemented each other. NRC performed the first and most important function by articulating a scientific program that captured the need for collective resources and focused efforts. OTA gathered information about bureaucratic moves and political choices more systematically and acted as a well-informed but neutral observer, expert in science policy rather than scientific strategies. When the NRC committee recommended organization under a lead agency but neglected to say which one, the mess was left for OTA to clean up. There was no avoiding the issue, since the interagency rivalries were well publicized and known throughout Congress.

In the end, no bill on interagency coordination became law, but the very real threat of legislation induced DOE and NIH to make peace. At the level of daily operations, there was never war; indeed, there was less conflict than often prevails between different institutes within NIH. The fact that *Science, Nature,*

and the *Washington Post* were following genome organization carefully undoubtedly made administrators think twice before acting upon their territorial urges. In the upper reaches of NIH and DOE, and among congressional patrons, however, talk of domination and potential conflict abounded. The process of achieving a suitable working arrangement between NIH and DOE took several years.

The battle was fought over two related Senate bills. On July 10, 1987, Senator Pete Domenici introduced S. 1480, the bill crafted by Jack McConnell and Domenici's staff to promote technology transfer from DOE-funded national laboratories.[12] In the section covering the genome project, Domenici's bill gave the Secretary of Energy a mandate to map the human genome. The Energy Secretary was to direct a research consortium dedicated to this purpose by chairing a National Policy Board on the Human Genome that included the NIH director, the NSF director, the Secretary of Agriculture, and other officials. Domenici considered adding the bill as an amendment to the trade bill then in the Senate. His staff called other Senate and House committees with jurisdiction. Senator Chiles, chairman of the NIH appropriations subcommittee and of the full Budget Committee, and Senator Kennedy, chairman of the NIH authorization committee, were in critical positions; their support was essential to pass the bill.[13–19] The Domenici bill was a surprise to most on the Hill, and even more of a surprise to the scientists who heard about it. After an initial blush of enthusiasm, Senator Domenici's office dropped the idea of adding it to the trade bill. The main reason was a roadblock thrown up by Senator Chiles. After a conversation with staff member Rand Snell en route from the Senate floor to another meeting, he said "it just didn't feel right" that DOE would lead the effort and NIH would not.[13; 14; 20]

Chiles was generally accepting of NIH initiatives in biotechnology. Through the tortuous connections of congressional politics, the genome project was linked to orange groves in Florida. Chiles's interest in biotechnology stemmed from a 1982 or 1983 meeting with a Florida constituent, Francis Aloysius Wood, dean of the School of Agriculture at the University of Florida.[13] Wood caught the senator's attention by describing how gene manipulation could move the frost belt sixty miles north. This meant more land could be devoted to cultivating a large crop of immense importance to Florida. Wood had found a graphic way to explain how deletion of genes that cause ice crystals to form on fruit, by recombinant DNA manipulations to create "ice-minus" bacteria, might lower the temperature necessary to cause fruit damage. If oranges could be grown in climes just a few degrees colder, it would reduce the annual worries of Florida's orange growers and would significantly expand the territory acceptable for planting. It was good for Florida; that was enough for the senator. The lingering message was the power of the new biology.

When the Senate majority reverted after six years to the Democrats in the 1986 election, Chiles ascended to chair of the appropriations subcommittee

that funded NIH. His main interest at NIH was biotechnology policy. The genome project became linked to biotechnology through Domenici's bill and some of the commercial rationale promoted by DOE, national laboratories, and NIH-supported investigators. When Domenici's office contacted Chiles's office about the DOE genome amendment to the trade bill, Rand Snell began to probe the network of scientific contacts around Chiles. Patricia Hoben from OTA happened to meet with Snell on the competitiveness of U.S. biotechnology. When she heard about the Domenici genome bill, Hoben mentioned there was already an OTA project on the genome project, of which she was also part, and asked whether there had been outside consultation with university researchers. Hoben suggested that Snell call Bruce Alberts in particular, as he was chairman of the NRC committee. Alberts was noncommittal, but did indicate that there was ambivalence about DOE leadership and a strong feeling among some on the NRC committee that NIH should be the lead agency.[20]

The *Washington Post* was one main reason the trade bill amendment died. Larry Thompson from the *Post* reported on the Domenici gambit on July 21, noting the year-long debate about NIH and DOE leadership. DOE "already has been aggressively pursuing the project," while Wyngaarden was "personally very interested in the genome project," yet "NIH's leaders have been criticized for waiting for the money to fall into their laps." Charles DeLisi, leader of the DOE program, shunted the issue aside, saying, "We are eliminating the debate by simply doing it."[4] The coverage provoked a storm of protest calls into Domenici's office, with spill-over into the Kennedy and Chiles bailiwicks.[13–16; 21; 22]

Domenici did not give up. He held a genome workshop in Santa Fe, August 31, 1987. It was Charles DeLisi's last day on the job at DOE.[23] Domenici pronounced his strong support for a DOE role in genome research in stentorian tones. At the meeting, Norman Anderson pulled out all the stops in a moment of zeal:

> I think so far as the man in the street is concerned . . . to say that here is the possibility at one shot of finding the cause of some 2,500 human diseases is really stunning. . . . A century from now, as history books are written, the big projects that were important in this century are the genome project, and after it possibly space and then the atomic bomb (the order of those, I don't know). But the man who first proposes to do the genome project in the United States Congress is in history.[24]

It was a good way to get the senator's attention.

Domenici and Wyngaarden came to loggerheads several months later. At hearings on Domenici's bill on September 17, 1987, Wyngaarden articulated his desire for what might be paraphrased as "the mission and the money, but not the management." This came during an exchange with Domenici following Wyngaarden's testimony:

> *Domenici:* If you were assured that it was not the intention of the legislation to in any way denigrate or detract from your ongoing activities, would you recommend that

the United States of America have a policy of mapping the human genome as expeditiously as possible?"

Wyngaarden: Yes, sir. Unequivocally, yes.

Domenici (several exchanges later): If Congress wants to do it, how do we do it? Just give the NIH more money under their existing program and give DOE some more money . . .

Wyngaarden: I think that is a very good way to do it.

Domenici: And would it get done?

Wyngaarden: Yes.

Domenici: Without any changes in the law?

Wyngaarden: I think so.

[James Decker, representing DOE, concurred with Wyngaarden.]

Domenici: I love you both and I think you are great. But I absolutely do not believe you. I believe it would get done. But I am quite sure that it would not get done in the most expeditious manner, because I do not think you would be charged with doing that. I do not think you would send up any requests of a priority nature with reference to it, because you do not have enough money to do what you are doing. And if you tried to send up the request, it would be thrown in the waste basket at OMB. . . .[25]

Wyngaarden and Domenici locked horns for several minutes more, over definitions of what the other had meant, but it was clear that the basic issue was one of mutual distrust between the legislative and executive branches of government. Congress, in the person of Domenici, did not trust the agencies to act quickly, and the agencies, principally in the person of Wyngaarden as supported by Decker, did not want to have Congress intruding into matters regarded as technical and scientific. Neither side could win decisively, and the policy process unfolded over many months of thrusts and parries.

The OTA report was released on April 27, 1988, at a hearing before Rep. John Dingell, chairman of the House Energy and Commerce Committee. Dingell was a powerful figure, with a reputation for hardball politics, and was in control of the committee engaged in much of the substantive legislation in the House. The focus of the hearing was how genome programs in two agencies could be integrated into a single project. In my testimony, I likened the situation of contending with genome projects to the problems facing Congress a century earlier, when trying to integrate the various surveys of land and coastal regions in anticipation of the second opening of the American West. We at OTA favored letting each agency contribute, but forging some interagency task force to coordinate efforts. If the project had started from scratch, it would indeed have been better to have a single lead agency with the vast bulk of budget control. But while NIH waited for a green light, DOE had mounted a substantial effort. The process of killing either effort would be politically costly and would serve mainly to undercut support for the resources needed to do the job overall. An interagency effort was suboptimal, but at least promised pluralistic funding and respite from internecine warfare. *Science* and

Nature coverage of the OTA report centered on interagency politics.[26–28] Well before the OTA report was released, Congress began to move on the issue.

When Chiles blocked Domenici's bill, Domenici was furious, but unable to maneuver around Chiles. As chairman and ranking minority member of the Budget Committee (Senators Chiles and Domenici chaired the committee under Democratic and Republican control, respectively), they had worked together on many issues. They decided to overcome their immediate feelings about Domenici's genome amendment and work toward an accommodation. Domenici shuttled the semiconductor, high-temperature superconductor, and several other provisions of his original bill (not related to the genome project) into the Defense authorization bill. Senators Domenici and Chiles worked with Senator Kennedy to patch together a separate genome bill. This became the Biotechnology Competitiveness Act of 1987, which included several biotechnology provisions in addition to the genome project. The Chiles-Kennedy-Domenici bill, S. 1966, included a genome project provision modified from Domenici's, most notably giving NIH and DOE joint leadership. The genome provisions focused squarely on interagency coordination and management.

Kennedy's position was critical as chairman of the NIH authorization committee. Kennedy was an opinion leader in the Senate on health and biomedical research, matters far less partisan than most others in the same committee (which also had jurisdiction over labor-related issues). Mona Sarfaty and Stephen Keith worked on several parts of the bill for Kennedy. Supported by the powerful triumvirate of Chiles, Domenici, and Kennedy, the bill sailed through the Senate, passing 88–1 (Senator William Proxmire was the lone dissenter).[14;29] Lisa Raines, working with staff for Kennedy and Chiles, polled the Industrial Biotechnology Association, a trade association for the larger biotechnology companies. The survey showed a strong consensus in favor of funding a genome project, but only under the aegis of NIH.[30] Snell noted, "This is a consensus bill. It's going to be difficult to do anything that sidesteps this." He neglected the always-simple option of killing it and the small matter of the House of Representatives.

After the bill cleared the Senate, it was sent to the House, where it was referred to the Energy and Commerce Committee and the Science, Space, and Technology Committee. The latter committee held hearings on the bill on July 14, 1988. It was a time of intense politicking between DOE and NIH, and the House committee was generally disposed in favor of the bill. At that hearing, I testified that the interagency committee specified in the Senate bill was one viable option, but it might be preferable to let NIH and DOE forge a workable coordination mechanism themselves, rather than impose a permanent and inflexible structure by legislation.[31–33] I thought the House might want to pass the bill to put pressure on the agencies, but then remove the interagency coordination structure from the bill in conference committee if NIH and DOE had by then reached some agreement. The bill was reported

out of the Science, Space, and Technology Committee favorably, and awaited action in Dingell's Energy and Commerce Committee.

NIH and DOE could have preempted genome initiatives in Congress by negotiating an agreement between themselves. Yet until the release of the NRC and OTA reports, and indeed for months after, staff from both NIH and DOE appeared to believe that Congress would somehow designate their agency the genome leader. The myopia of those working for one agency or the other was reinforced by internal conversations with different constituencies that did not overlap significantly. DOE was fostered by the national laboratories, while NIH had its university-based investigators. The bureaucracies heard only the messages passing through their separate constituencies. In conversations with congressional staff, including me, both DOE and NIH representatives voiced disappointment that NRC and OTA ducked a tough call (that is, choosing their agency to lead); yet there was no call to make. The existence of twin genome programs was set as soon as DOE got its first authorization and appropriation through Congress and as long as NIH decided not to abdicate its role. There were forces in both agencies moving toward accommodation, but they did not quite find their way to successful completion until faced with the prospect of legislation.

DOE and NIH vied for advantage from the summer of 1986 until well into 1988. After NIH missed the first Santa Fe meeting in March 1986, NIH and DOE consistently sent representatives to each other's meetings through 1987 and 1988. This was no small commitment. Genome meetings proliferated as more and more players sought a voice, and DOE and NIH were both represented at each meeting—NRC committee meetings, OTA panel meetings and workshops, and a myriad of others. The profusion of meetings brought staff at the program level together frequently, and they maintained cordial relations. Irene Eckstrand of NIGMS sounded a conciliatory note in a memo reporting on the HERAC subcommittee meeting in February 1987. She observed that "the subcommittee and OHER staff are clearly committed to this project and seem committed to working with other agencies. They are anxious to learn NIH's plans and stated their view that NIH should be more actively involved."[34]

At the level of agency heads, David Kingsbury of NSF emerged as a mediator for a time, attempting to channel the conflict, first through the Biotechnology Science Coordinating Committee in the White House (formed principally to deal with interagency disagreements over the release of genetically altered organisms into the environment) and then through the Domestic Policy Council (a cabinet-level group).[6; 35; 36] Kingsbury's mediating role meant that NSF had to stay out of the direct competition. NSF's policy position was quite clear for several years—it had no genome program *per se,* although NSF support for instrumentation and nonhuman biology was directly relevant. It was a position crafted in the bureaucratic netherworld where incompatible concepts

reside comfortably in the same paragraph. In Washington, this was not only acceptable, it was occasionally compulsory.

Kingsbury's political base eroded quickly when he was implicated in a financial conflict of interest. The Department of Justice began an investigation related to his financial connections with Porton, Inc.,[37] a biotechnology and instrumentation company. NSF was thus taken out of the loop for several years, and it reentered only in 1989 with its instrumentation centers and plans for a plant genome research focused on *Arabidopsis thaliana,* a plant with a conveniently small genome and short generation time.[38] NSF thus entered the genome sweepstakes late, at least as a declared contestant, but on a strong base in plant science and instrumentation.

At NIH, Wyngaarden had to make a clear choice between creating a special genome effort or maintaining the *status quo ante,* but with a larger budget for genetics. Wyngaarden became chairman of the Domestic Policy Council genome working group, which at its May 5, 1987, meeting decided to survey its members about their spending for genome research.[39] He was thus at once at the nexus of a dispute about genome project administration within the NIH and also an arbiter of NIH's role relative to DOE. Incompatible visions of what the project entailed kept NIH and DOE apart. The seed for this disagreement was the genome research funding information so meticulously gathered by Ruth Kirschstein.

Kirschstein was keen to protect basic genetics research from a political juggernaut. NIGMS was the largest source of funding for basic genetics in the world. She led the effort to retain NIH leadership under a regime that would expand funding for genetics research. Her response to genome enthusiasm was to enlarge the pie while retaining the existing NIH bureaucratic structure. The NIH funding figures were her main tool. She noted that NIH funded $313 million in fiscal year 1987 on projects that involved mapping or sequencing, of which just over $90 million was for work in humans. The NIGMS program announcements demonstrated a willingness to support genome research, but did not formally set aside funds for this purpose. She argued that the announcements were "not exactly business as usual, but not highly targeted either." Rachel Levinson, staff to Wyngaarden, whose job included genome policies, corroborated this, arguing there was no need "for a concerted effort because it is not new. Every institute has work related to mapping and sequencing."[6]

Kirschstein's data-gathering showed the robust science base NIH was laying in genetics, but her interpretation of the data dismayed those who wanted a genome mapping and sequencing project, as opposed to a series of individual gene hunts. Several members of the NRC committee, among them Watson, wanted to recommend NIH leadership outright. Before they could take such a position, however, they needed some indication that the project was understood and supported at NIH. They wanted NIH to push vigorously for complete genetic and physical maps and development of new technologies. David

Botstein, another member of the NRC committee, felt strongly that NIH had neglected RFLP mapping, and he wanted a clear signal of support. In the eyes of several committee members, NIH did not need to take any position about the DOE initiative, but merely to make a commitment to a concerted research program. NIH would then emerge as *de facto* leader by virtue of its scientific preeminence and overwhelming size advantage.

Kirschstein's expand-the-pie-but-don't-fire-the-cook position was intended to assuage fears that genome efforts would threaten investigator-initiated research. Her constituency included those pursuing individual research projects in genetics and basic research. The constituency favoring the genome project was, in contrast, many senior and powerful opinion leaders in molecular biology. Kirschstein's positions were cold comfort for them. The position that NIH was already committing hundreds of millions on genome research and the implied failure to distinguish individual gene hunting from global genome mapping undermined support for NIH leadership. The concern was based in part on NIH's historical failure to support genetic linkage maps in the

Ruth Kirschstein, as director of the National Institute of General Medical Sciences at NIH, presided over the science that spawned the genome project. Her vision of how to conduct the project ultimately lost out to that of James Watson and the NRC committee, and the new NIH genome center was, in effect, carved out of her institute. *Courtesy National Institute of General Medical Sciences*

early 1980s and in part on the NIH's own justification documents. In the same memo that presented the figures on NIH genome research, for example, three projects were listed to indicate the kind of work that might be undertaken with further genome funding. All three projects were searches for individual genes: the retinoblastoma gene, the gene for Alzheimer's disease, and a gene impli-

cated in autoimmune disease.[40] These were important targets, and indeed all were hotly pursued over the next year by NIH researchers, but they were not what the committee had in mind when it asked for a comprehensive genome map. Small project grants of themselves were not enough; the problem was not what NIH was doing, but what it had so far failed to do.

Kirschstein's position was a delicate one. Her institute based its reputation on supporting the best basic research throughout the country. NIGMS had no in-house research program on the NIH campus, unlike most other institutes. It was the very success of the NIGMS grants program that kindled the idea of the genome project in the first place. Kirschstein's position was aimed at preserving a strong base for undirected research. This put her in conflict with those, such as Watson, who argued that genetics now demanded a more deliberately planned and coordinated approach, with attention to technology development and completion of maps. At root was a disagreement about the best process for investing public funds in the future of genetics. Kirschstein believed that a large genome program could well cut into the core of undirected research; such a program was inimical to the style of managing grants in her institute.

Contentiousness was apparent at an August 1987 OTA workshop. Dave Guston, working with us at OTA as a summer fellow, arranged the meeting (originally suggested by Rachel Levinson of NIH) to project the costs of genome research. Nobel laureate Paul Berg chaired the meeting. After a long day trotting through the various component items necessary for a genome program, the group addressed administrative costs. Watson recounted that he had urged Wyngaarden to set aside genome research funds in the director's office. Kirschstein responded that the first genome moneys, then still awaiting final action in Congress, were initially considered as an add-on to the director's office, but Wyngaarden had subsequently assigned them to NIGMS. She noted there was an internal NIH working group and that there had been several program announcements.

The tension between Watson and Kirschstein was palpable. Kirschstein noted that "we sent them [program announcements] out to people who don't bother to read them when we send them out to them . . . people don't seem to realize that we want to do this. I don't know how to get the word across."[41] Minutes later, Watson came back to program administration, asking: "Are we going to have a large program run by a committee, or is there going to be one person who is in charge of it? I instinctively believe one person should be in charge of it who understands the scientific issues and who is not chosen purely to be an administrator."[41] Walter Gilbert supported Watson's notion that there had to be much more than a grant program, or the map and sequence data would never coalesce into useful maps and databases. The conversation drifted to other topics, but again Watson snapped back to his foremost concern. He aimed a question at John Sulston, directing the physical mapping effort on *C.*

elegans: "Doesn't one person really have to finish up that last 10 percent and live or die for the thing?"

Sulston, finding himself unexpectedly invited into the crossfire, temporized until he could gather his wits. "Yes, I expect so . . . you can have your political division into chromosomes . . . I don't see how you could ever have a number of labs generating raw data and fitting it all together." He then wondered whether sequence data from separate laboratories might indeed be pooled in a way impossible for physical mapping data.

Watson was talking about something altogether different, however. "You're going to get bad years, and the program will be under attack, and there's got to be someone who sees all the components and fights for it."

Sulston then worried about one person "administering this huge empire. Do you really want that?"

Watson didn't miss a beat. "I think someone has got to do it."

Sulston shot back, "You would like to do it."

Watson ducked. In a manner befitting a political figure, he offered up a non sequitur: "It's a question whether it's an active scientist or a retired scientist."

Sulston then elaborated how it was important to cultivate "individual dreams . . . surely that is the way to do it."

Watson then interjected a humorous deflection. One of Watson's heroes was Franklin D. Roosevelt, a master of deliberate inscrutability. Watson's next remark would have done Roosevelt proud. "Well, I couldn't think of a job I'd like less. I'm very relieved." The exchange broke up in laughter. Leroy Hood suggested that instead of a scientific director, perhaps the chairman of an advisory panel could serve this purpose. Kirschstein then stepped in, noting an outside scientist was already on the panel (referring to George Palade, a Nobel laureate from Yale). Watson shot back, testily: "That sounds good, but he has no qualifications for the job at all." Kirschstein bristled: "Well, he thinks pretty well."[41]

Paul Berg drew a halt to the swordplay before someone lost an arm. He asked me to summarize congressional interests. I noted that Congress was working on legislation directly concerned with how the project would be coordinated between NIH and DOE, referring to the Chile-Kennedy-Domenici efforts then beginning to take shape. Berg adjourned the workshop, noting that debate about genome research had shifted in the year since he and Gilbert had chaired the Cold Spring Harbor meeting. The question had moved from whether to how.

In later conversations, both Kirschstein and Watson recalled the meeting with residual anger. They had incompatible visions of how the genome project should proceed. It was a clash between two of the most powerful figures in molecular biology. It was science policy formation at its passionate best; each champion cared about and fought for a persuasive vision. But only one could

prevail. John Sulston had sliced to the heart of the matter. Watson would be king.

In late 1987, after the Wyngaarden-Domenici and Watson-Kirschstein contretemps, NIH vigorously opposed the Domenici bill. In a letter drafted for the Secretary of HHS, attached to a memo drafted by Kirschstein, NIH made clear its opposition to the bill because it gave leadership to DOE and did "not fully recognize the importance of research in genetics to human health and the dimensions of the historical and continuing commitment NIH has made to such research."[42]

As the NRC and OTA reports came out in 1988, NIH and DOE were faced with two options: conspicuous cooperation or a strong likelihood of legislation that embodied Congress's preferred framework. In December, James Decker, acting director of the Office of Energy Research at DOE, wrote to Wyngaarden seeking some agreement between the agencies.[43] There is no reply letter in the NIH files, and DOE officials reported never having received an answer. After a December 1987 meeting between Watson and Wyngaarden, while the NRC report was nearing completion, momentum seemed to favor NIH. NIH thus had little to gain by such an agreement at that time, and Congress might yet declare NIH the leader. If there were to be a single lead agency, it had to be NIH, and the OTA report said this quite plainly. Events did not conform to NIH's highest hopes, however.

NIH and DOE had to settle into a permanent peace. Judith Greenberg, new director of the genetics program at NIGMS and a chief in the Kirschstein tribe, proffered an olive branch in the *Washington Post,* noting "there's certainly room for more than one agency. . . . The National Science Foundation, for example, has supported a lot of research that is closely related to the research that NIGMS supports. In fact the two have a way of complementing each other, and I don't think there should be any difference with the DOE-NIH cooperation."[44]

Greenberg's sanguine views began to dominate as 1988 drew to a close. NIH's program would be significantly larger, but DOE would also have a substantial budget. In light of the standoff, the agencies opted to sign a memorandum of understanding, in hopes of staving off House action on the bill. They reached a tacit agreement with Lesley Russell from the Energy and Commerce Committee, and the committee never reported the bill for a floor vote. The content of the memorandum was less important than agreement on a process for joint planning, forcing NIH and DOE to face the political reality that the other would also have a genome program.

There was one more way that Wyngaarden could assert leadership, however, and he exercised this option with a masterful stroke. Wyngaarden established a bureaucratic center for genome research, and he secured the all-important budget. Wyngaarden was best remembered, however, for a single personnel decision, the appointment of James D. Watson to direct NIH's genome effort.

13

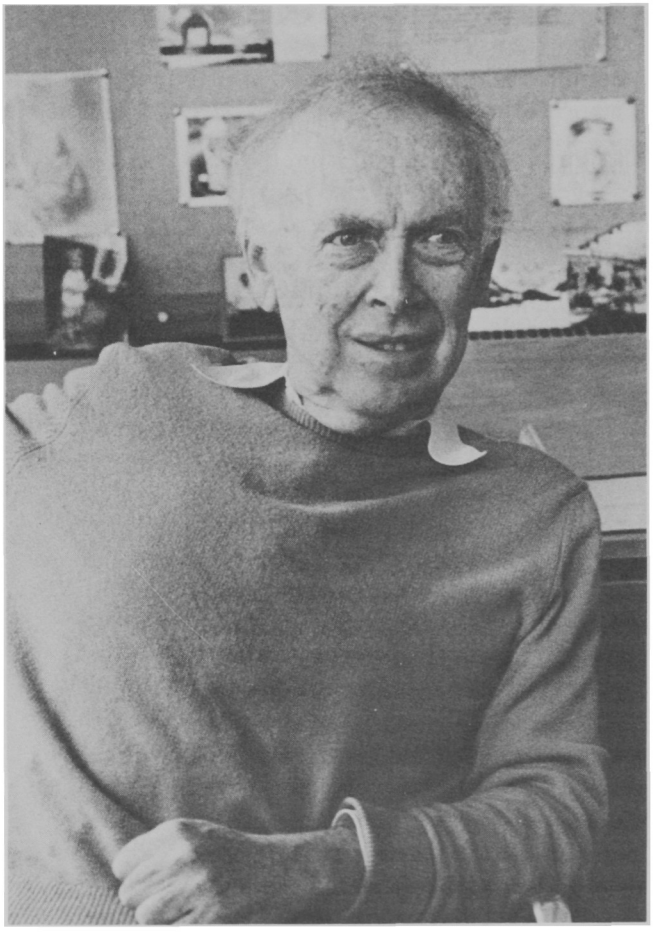
Honest Jim and the Genome

During 1988, Jim Watson emerged from the back room to tower over the genome project. Watson seized the moment, noting, "I would only once have the opportunity to let my scientific life encompass a path from double helix to the three billion steps of the human genome."[1] As presaged at the 1987 OTA workshop on costs of the genome project, Watson became head of the NIH genome office. By this stroke, NIH director James Wyngaarden assured NIH a dominant voice in genome politics. It was a strong voice, but not necessarily in close harmony with the others. Bob Davis of the *Wall Street Journal* remarked on Watson's distinctive tactics: "Taunt the Germans for their fears about science, bash the Japanese for 'freeloading,' and dish out money to your opponents to knock the program."[2]

Watson was among the world's most famous scientists, surely the best-known biologist of the day. Upon his appointment, attention naturally gravitated toward him. His every word was taken as an NIH policy statement. Although his direct authority extended only over the NIH program, the scope of Watson's informal influence was far vaster. As Norton Zinder of Rockefeller University expressed it, Watson was "standing like a colossus over the whole program."[2] By appointing Watson, Wyngaarden made NIH the center of power in genome politics and harnessed one of the dominant talents in molecular biology.

Watson's authority was rooted in history, as codiscoverer of the double-helical structure of DNA, one of the most significant revelations in twentieth-century biology. His influence also stemmed from a reputation for having an extraordinary nose for the important questions of biology. Watson made a big impact as an impresario of molecular biology. At Harvard in the 1960s, he pulled together one of the "hot" laboratories in molecular biology, one of the "big three," standing beside the MRC laboratory in Cambridge and the Pasteur Institute in Paris. He became the director of Cold Spring Harbor Laboratory in 1968. The laboratory had been rescued from financial oblivion by his predecessor John Cairns. Watson took a quiet institution and made it a robust world center of molecular biology.[3] Watson's personal energy and focused commitment were the ultimate sources of power.

Watson's scientific and administrative careers were built on an independent sense of priorities. "Just do good, and don't care if it doesn't seem good to others."[4] His highly intuitive manner focused on character judgments and results, and scientific results were the ones that counted most. Good science was elevated to a guiding moral principle. Watson's credo was that "the essence of most good science is very deep curiosity with some way of knowing the comparative importance of things you are curious about."[5] His ability to ferret



James D. Watson set in motion the whole chain of events that led to the Human Genome Project when he and Francis Crick discovered the double-helical structure of DNA in 1953. The longtime director of the Cold Spring Harbor Laboratory, he served as the first head of the NIH genome program, from October 1988 to April 1992. *Courtesy Cold Spring Harbor Laboratory Library*

out the central problems of molecular biology was legendary; it ranked as a salient quality along with an almost reckless openness and a brutal honesty.[5–7] Watson moved institutions to stay atop the rapidly shifting sands of science. "The one word that comes to mind on Jim as an administrator is bold," noted Ray Gesteland, Watson's former student.[5]

In October 1988, Watson accepted an appointment as associate director of NIH and head of the Office of Human Genome Research, housed in the

NIH director's office and answering to NIH director James Wyngaarden. Watson's boldness rose to the surface immediately. At the press conference to announce his appointment, Watson declared that the ethical and social implications of genome research warranted a special effort and should be funded directly by NIH.[1;8] In making this path-breaking commitment, he took a leaf from the National Research Council and Office of Technology Assessment reports. This was nonetheless an astonishing event. While NRC and OTA had indeed suggested that analysis of social, ethical, and legal implications of rapidly advancing human genetics should go forward in parallel with genome research, it was still surprising to be taken seriously, particularly by Watson, whose public image as an *enfant terrible* did not meld well with support for careful deliberation and expenditure outside science. Remaining in character, he made the public commitment before conferring with Wyngaarden or anyone else at NIH.[9]

Watson first got interested in genetics late in his undergraduate years as one of Robert Maynard Hutchins's "Whiz Kids" at the University of Chicago.[10] He was fortunate to choose the University of Indiana for his graduate work, when Harvard and the California Institute of Technology rejected him.[7] At Indiana, he found Salvador Luria, who became his mentor. In April 1948, Max Delbrück came to Bloomington, and he deeply impressed Watson. Delbrück was the philosopher-king of the "phage" group, which studied viruses that infected bacteria, among the smallest of living things, chosen because their biology was amenable to approach through precise experimental formulations. The phage group included Delbrück, Luria, and Alfred Hershey. The phage group's central thesis pursued the line laid out by physicist Erwin Schrödinger in his book *What Is Life?*[11;12] Life could be explained by chemical mechanisms.

Delbrück was an erstwhile physicist turned biologist. His guiding principle was to study systems simple enough to explain by molecular mechanism, and to explain function by elucidating structure.[13] The ideal experiment was one that had a simple yes or no answer and shed light on molecular mechanism. Molecules, cells, and life were elements in a reductionist dreamscape.

In the summer of 1948, Watson and another student, Renato Dulbecco, went with Luria to Cold Spring Harbor Laboratory, summer home to the phage group.[10] During his graduate work, Watson became convinced that the structure of DNA held the key to understanding important questions of molecular biology. This was not yet a widely shared belief, but it was becoming a central premise of the group surrounding Watson.[14]

Watson was fortunate to happen upon Francis Crick, who shared his passion for DNA. Crick later reflected: "It's true that by blundering about we stumbled on gold, but the fact remains that we were looking for gold. Both of us had decided, quite independently of each other, that the central problem in molecular biology was the chemical structure of the gene."[15] About Watson,

he commented, "He just wanted the answer, and whether he got it by sound methods or flashy ones did not bother him one bit. All he wanted was to get it *as quickly as possible.*"[15] Watson's taste for important problems was established early. His signature was also quickly established: choose a scientific goal and push toward it relentlessly. He adopted any method that looked promising, regardless of its disciplinary origin or the politics of its genesis.

The double helix became the central icon of molecular biology. The discovery was important of itself, but Watson thrust it into the public eye by writing *The Double Helix,* a young man's chronicle of the process. The book, written in the years after Watson, Crick, and Maurice Wilkins received the Nobel Prize in 1962, became a best-seller because of its lively and personal tone. The literati loved the book; those who wanted to preserve the image of selfless scientists pursuing knowledge for its own sake hated the book and vilified Watson for writing it.[14] Watson self-consciously cast himself as the antihero, a compulsively competitive brash cynic obsessed not only with DNA but also young women's chests and backsides. The inglorious image he projected in *The Double Helix* haunted him for life. It was the persona that others expected to encounter, and projected on him. He explained away this unflattering self-portrait as driven by his desire to tell a racy tale.[16] If he made himself a hero, his story would be undermined. To preserve the liberty to be nasty to others, he was nastier to himself. David Schlessinger, a former student, noted that "critics who ordinarily suspect any autobiography of distortion have swallowed the novel whole, apparently because the author has been so 'honest' about himself."[17] Schlessinger called the book a novel; Crick likewise reflected that Watson did not truly resemble the monomaniacal Nobel aspirant portrayed in *The Double Helix.*[15; 18]

Watson started *The Double Helix* by recounting how Willy Seeds snubbed him on a walk in the Swiss Alps. Seeds asked, "How's Honest Jim?" and walked on by. *Honest Jim* was the working title of Watson's book, cadged from Kingsley Amis's then-current novel *Lucky Jim. Honest Jim* remained a nickname of sorts for Watson thereafter, for many years mainly as a term of derision. Those who worked closely with Watson recognized a kernel of truth in the epithet. It captured one of Watson's dominant qualities, his unremitting candor, both admirable and at times vexing. Watson exercised it vigorously, often exploding at students and telling his administrative superiors precisely what he thought. He could be petulant, at times almost vindictive. Watson long remembered swearing at the president of Harvard when he was passed over for tenure.[4; 19] He used his fame as the raging bull of molecular biology to feed his power and did not hesitate to tramp onto politically muddy turf. He dubbed Nixon's War on Cancer "lunacy" in the early 1970s, for example.[20] But quips and tirades were not Watson's main contribution. Such quirks were cultivated eccentricities, freedoms earned by making a great discovery at age twenty-five. The hard thing was to prove it was not a fluke.

Prove it he did. First at Harvard and then at Cold Spring Harbor, the

scientific results flowing out of his laboratory showed that he was more than a person who happened to be in the room when Francis Crick was about. More important, he trained a cadre of researchers who subsequently proved their worth, and who now reflect on him warmly.[21] He created a laboratory pedigree as impressive as any in molecular biology. During the 1960s, he slowly grew out from under Crick's shadow in his own mind.[4; 10] Others also took note. In September 1962, Watson and David Rogers were the only biologists on *Life* magazine's roster of the hundred most important men and women in the United States.[22] In 1990, Jonas Salk and Watson were the only biologists to earn a place among *Life*'s hundred most important Americans of the century.[23]

While Watson's public persona was defined by his self-portrait in *The Double Helix,* his impact on molecular biology came through another book, *The Molecular Biology of the Gene.*[24] Almost to a person, molecular biologists over the age of forty-five anywhere in the world can recall where they were when they first read the book. It was an unusual text, a book strongly written by a single author who was pushing a line of argument. It was authoritative, but willing to call on intuition and to piece together plausible, if not fully demonstrated, results to tag the most important and central scientific questions facing molecular biology. This book earned him the admiration of a generation of scientists, the first to grow up in thrall to molecular biology.

Watson had an aptitude for teaching himself new skills. He learned how to write well in the popular voice as he worked on *The Double Helix.* He made another career as textbook author, moving *The Molecular Biology of the Gene* through three editions that all sold well,[25] and helping to edit several other scientific texts. He mastered an entirely different set of skills to raise millions each year for Cold Spring Harbor Laboratory. His talents were highly plastic. With the Human Genome Project, he turned his talents to national politics—science policy Washington-style.

As 1987 gave way to 1988, Wyngaarden was beset by disagreement about the proper strategy to pursue for genome research. Ruth Kirschstein and Jim Watson favored incompatible administrative options, exemplifying an ideological rift within the biomedical research community. Wyngaarden had to choose. Watson and Baltimore met with Wyngaarden on December 17, 1987 to discuss AIDS research and the human genome. Watson forcefully expounded his view that NIH had missed the boat on the genome project; he railed against Kirschstein's stay-the-course approach. The next day, Wyngaarden met with NIH staff to convene a planning meeting in Reston, Virginia. That meeting became the pliers to extract an NIH commitment.

There was extensive overlap between those invited to the Reston planning meeting and the membership of OTA and NRC committees. The NRC report was released with a great ballyhoo in February, and many of its members participated in a session at the AAAS annual meeting in Washington. After that session, a group got together and decided they were not interested in

coming to NIH again to urge a major commitment, with no assurance of a response. Charles Cantor, who had been sent the draft agenda for the upcoming Reston meeting, believed a tentative tone would appear in disastrous contrast to the enthusiasm so pervasive in the wake of the NRC report. He called Rachel Levinson, the staff person most responsible for planning the Reston meeting, to sound the alarm.[26;27] Victor McKusick was testifying at the same hearing as Wyngaarden the following week. Wyngaarden called McKusick to discuss what they would say. McKusick suggested a model of funding similar to that used for sustaining research infrastructure, through NIH's Division of Research Resources. Wyngaarden followed up with calls to several others from the NRC committee who had been at the AAAS meeting. He got readings consistent with McKusick's.

Rachel Levinson completely revised the format of the meeting, less than a week before it was to take place.[26] The purpose shifted from seeking consensus about whether NIH should proceed to planning how best to do so. The Reston meeting took place from February 29 to March 1, 1988, and refined the scientific framework laid out in the NRC report. With the backing of an NRC report, the kernel of a coherent scientific plan, and congressional signals auguring well for substantially increased appropriations in future years, Wyngaarden chose the high road.

A group met with Wyngaarden during a lunch break at the Reston meeting. They waited for Watson to leave before starting the discussion. They indicated that Watson was the only person who could credibly lead the NIH effort.[26;28–30] Watson's involvement would enshrine the project as first-class science. He would bring his prodigious organizational talents to NIH, and his status as the discoverer of DNA would carry considerable weight on Capitol Hill. Wyngaarden had already been thinking about Watson before the meeting. Following that meeting in Reston, Wyngaarden was widely known to be considering Watson as the head of genome efforts at NIH.[31] At Reston, Watson agitated strongly for the same goal he stated at the OTA workshop seven months earlier—for NIH to leave its genome effort in the hands of an active scientist. He later noted, "I did not then realize that I could be perceived as arguing for my own subsequent appointment."[1] One could be forgiven for thinking Watson was not so naive; John Sulston had months before pushed him publicly on precisely this point.

Expected or not, it was uncharacteristic of Watson to care what others thought when an important goal was at stake. "Just do good, and don't care if it doesn't seem good to others." He wanted the job done right. In October 1988, he agreed to start directing NIH's genome program, which took shape as the NIH Office of Human Genome Research.[32–34] The *New York Times* commented that "the appointment seemingly completes his metamorphosis into a senior statesman of science."[35]

Watson hired two NIH stalwarts, Elke Jordan and Mark Guyer, from the National Institute of General Medical Sciences (NIGMS). Jordan and Guyer

carried out most of the work in the new NIH genome office as its first full-time staff. Jordan had directed the genetics program at NIGMS. Watson knew her from the 1960s, when she was a molecular biologist working in Matthew Meselson's laboratory, down the hall from Watson at Harvard. Guyer, an erstwhile bacterial geneticist trained at Berkeley, had worked at Genex Corp, before joining NIGMS.

NIH and DOE signed a memorandum of understanding in the fall of 1988, to avoid the threatened Chiles-Kennedy-Domenici bill. The memorandum ratified an existing informal arrangement, but grew into substantially more, as bona fide joint planning came to seem advantageous to both agencies. Throughout 1988 and 1989, staff at NIH and DOE met to discuss how to carry out the terms of the memorandum. They appointed a joint NIH-DOE advisory group, comprosed of members taken from the advisory panels for each agency.

Randy Snell, from Chiles's personal staff, and Michael Hall, staff director of the NIH appropriations subcommittee, inserted language into the conference report for the fiscal year 1989 appropriation, a document that accompanied the law to explain congressional intent. The conference report expressed concern about interagency coordination and stipulated that NIH and DOE report back to Congress "the optimal strategy for mapping and sequencing the human genome."[36] Watson insisted on responding with a "serious" planning document, rather than a coordination plan that worked only on paper.

For many months, an informal coordinating committee met monthly to make the logistical arrangements among the various agencies and organizations. Mark Guyer, Diane Hinton of HHMI, Irene Eckstrand of NIGMS, John Wooley of NSF, and Ben Barnhart of DOE formed the core, and others attended occasionally. Their plans began to jell when combined with the powerhouses of genome research in a retreat at the Banbury Center, Cold Spring Harbor Laboratory, August 28 to 30, 1989. The advisory committees and staff for both DOE and NIH, and a few additional experts in genome research, began to plan in a truly cooperative mode.

Norton Zinder, chairman of NIH's genome advisory committee, organized the discussion into task areas. Working groups were asked to specify goals and means of achieving them. Much of the meeting focused on how to construct physical maps. Maynard Olson and others concentrated on the idea of using short stretches of DNA sequence as unique "tags" that would serve as landmarks on the chromosomes. Laboratories using different methods could thus compare results directly. Cassandra Smith raised the idea of using sequence information as an index earlier that year at the Cold Spring Harbor symposium. Olson and Botstein hammered the notion home at Banbury, stressing its importance as a common reporting language to unify physical and genetic linkage mapping. Unique short DNA segments of known sequence could bridge the two kinds of maps and also link them to DNA sequencing as mapping moved toward its ultimate level of resolution. The idea was seized

upon and given the name Sequence-Tagged Sites (STS). A group agreed to prepare a paper for *Science*.[37;38]

NIH and DOE staff hoped to prepare a five-year plan going into the meeting, but uncertainties about the proper strategy held their aspirations in abeyance. The genome project could yet become an amorphous grand idea of imprecise scope and indefinite goals. Barnhart and Zinder thought that no specific planning draft would emerge from the retreat,[39] but they proved themselves wrong. The plan took shape after the retreat, and staff adopted the goal-directed format to focus the report.[40;41]

The NIH genome office had planning capacity, but still lacked direct budget authority. Watson, Jordan, and Guyer put together a genome advisory body, linked NIH to DOE, and began to plan how NIH might best contribute to genome research. Statutory authority to spend federal funds remained with the NIGMS council. The difference was largely symbolic, as NIGMS staff and council cooperated closely with their former colleagues. The character of the genome project was drifting away from its traditional NIGMS moorings, however, and budgetary independence was an important step in this process.

A year after the NIH genome office was created, as the budget grew to $59.5 million for fiscal year 1990, the Office of Human Genome Research became the National Center for Human Genome Research (NCHGR), with Watson as director. Louis Sullivan, Jr., Secretary of Health and Human Services, conferred center status on the genome project.[42] NCHGR thus gained direct control over its budget, similar to the authority wielded by other NIH institutes, centers, and divisions. Mark Guyer announced at the 1990 NCHGR Christmas party that staff had grown from two to twenty-two or twenty-three in a year (depending on whether I counted as an outside consultant).

Watson had made another career shift to direct a part of the federal bureaucracy. He was an unusual director. Watson's stature as a scientist and public personality was his power base; his NIH duties were almost incidental by comparison. Unlike other NIH institute and center directors, he did not come to power by dint of position, but tapped directly into the community supported by NIH. He used his status as the "father of DNA" to secure resources from Congress and to guide the scientific strategy of genome research. Stephen Hall noted in a *Smithsonian* profile that "it is precisely Watson's candor and integrity, and his willingness to take the heat," that earned support among his colleagues.[6] He now used the same tactics in Washington.

Watson declared *ex cathedra* that the genome project would officially start in October 1990, at the beginning of fiscal year 1991. He argued that the first few years were taken up by getting organized. Strong crosswinds hit the genome project as it lifted off the runway. A battle over the 1991 budget severely tested support for the project.

The early stages of the budget year looked promising. NCHGR requested $108 million (up from $59.5 million), and the genome office at DOE sought

$46 million (up from $26 million), getting within range of the aggregate $200 million plateau foreseen in the NRC plan. If both agencies got their requested budgets, the budget target would likely be reached in 1992. At that point, the high-growth phase could stop, leaving the programs on a firm footing and less conspicuous as targets for budget cuts. Initial budget requests survived departmental and OMB review; indeed, they drew strong support, but a storm was brewing outside.

The problem first surfaced at House appropriations hearings.[43] Congressman Obey took Watson to task for failing to find a way to prevent genetic information from being abused by insurance companies and employers. Obey asked: "What can you point to besides your personal hope" that abuses would not occur? He continued "wondering if whether we would really be doing any great long-term damage if we were to go to $100 million of money to go to R01s [individual investigator-initiated grants]" and warned, "I think you should not underestimate the weakness of the political system in terms of its ability to deliver the kind of protections that need to be afforded this information."[43] Throughout the hearings on various NIH institutes, it was clear that the committee was looking for loose change, and would give programs with either large budget increases or heavy reliance on research centers careful scrutiny, in strong preference for support of R01 grants.

The genome budget was growing very rapidly as a percent of its 1990 base, and it was set to establish centers as a foundation for its future work. The 1990 budget already included some funds for genome research centers, but 1991 was the year the center program was to expand considerably. Rumors that the budget was in trouble reached NCHGR a week before the House subcommittee was to consider the final budget marks. Watson and Jordan went to Capitol Hill to meet with Michael Stephens, chairman Natcher's aide, who handled the NIH budget in the House of Representatives. Watson was extremely discouraged, and he threatened to resign in a stormy meeting. Stephens and Natcher were unimpressed.

The genome budget's growth phase coincided with a drop in the proportion of grants funded during each review cycle. This stemmed from several policy decisions taken by NIH beginning in 1986. That year, NIH began to respond to a chorus of voices from the scientific community by agreeing to extend the length of the average research grant. The idea was to free investigators from perpetual fund-raising, giving them a year or two of working budget without the distraction of filing new grant applications. In the standard three-year cycle, an investigator would work for a year, then begin to write grants during the second year, so that there would be funding when the third year ended. New proposals thus began with only a year's new data; investigators spent inordinate energies as supplicants for money, and the system encouraged a proliferation of proposals to hedge bets against uncertainty. If the grant period was extended to five years, the argument went, then investigators should be able to work relatively worry-free for three years, and would have to

apply only 60 percent as often. This would increase productivity and reduce instability.

Lengthening the grant period meant, however, that the carryover commitments for old grants would mount each year until a new equilibrium was reached. This necessarily cut into the amount of new funding available each year. Carry-over commitments increased from 67 percent of the NIH budget in 1985 to 76 percent in 1990.[44] In the long run, fewer applications would be expected, as the stability of the five-year cycle caught hold. In the interim, however, the number of new grants would necessarily fall. The effect of longer grant commitments was exacerbated by an increase in the average yearly award, because of inflation of research costs. From 1982 to 1990, the average length of award increased 23 percent, from 3.3 to 4.3 years, and the average commitment for each grant increased from $107,000 to $208,000, a 94 percent increase.[45] Most of the increase was due to rising personnel costs.[44] Thus because of both the greater length and higher annual costs of grants, the number of new grants dropped from a third to a fourth of total applications. Moreover, the expected drop in new applications from grant term extension, which should have been felt by 1989 as the 1986 policies took effect, never materialized. The number of new applications stayed the same, even as the number of new grants that could be funded dropped.[44]

New scientific vistas were opening in almost every field, but confronted worsening funding prospects. This translated into immense frustration. Some investigators went hunting for a scapegoat. There was some sniping at AIDS, which accounted for roughly 10 percent of the NIH budget, but invective was also directed at the genome project. The genome project was vulnerable, as it lacked a disease constituency and its bureaucratic base was as yet small and feeble. Its indomitable director, however, was not.

University-based research centers, as opposed to individual project grants, were under attack throughout NIH, as scientists supported by small independent grants felt squeezed. The House Appropriations Committee responded by setting a cap for all centers at NIH and calling for review of the proposed genome centers. It gave NCHGR $71 million for fiscal year 1991, enough to carry forward its previous commitments, but with few funds for new grants or centers. It also left an additional $18 million available for genome research, but gave authority to spend it only to a permanent NIH director.[46;47] There was no permanent NIH director, nor would there be one soon. Wyngaarden had resigned in July 1989 to join the White House Office of Science and Technology Policy, and the NIH director's position remained vacant until Bernadine Healy was confirmed by the Senate on 9 April 1991.[48] The budget set-aside was a shot across Watson's bow. It signaled congressional ire that the administration had failed to appoint an NIH director, and clipped Watson's wings. A fourth of his budget could be held hostage to a political process well beyond his control. His threat to resign was not appreciated. The tactic that

worked well at Harvard and Cold Spring Harbor, where losing Watson was a serious threat to the institution's prestige, did not work nearly so well in Washington.

Meanwhile, opposition mounted among investigators, particularly young ones, within the research community. This opposition was independent of the House Appropriations Committee's concerns, and centered on a different, although related, set of issues. Watson's former mentor Salvador Luria wrote a blistering letter to *Science* asserting that "the program has been promoted without public discussion by a small coterie of power-seeking enthusiasts."[49] One could only wonder why he couched his judgment in the plural, as the target was so clearly Watson. The problem with Luria's statement was not its accuracy. There were indeed enthusiasts, and they were seeking power. The sting of his judgment was, however, that they were using the genome project to seek power, rather than using power to get the genome project. This was a motivational judgment Luria was poorly situated to make.

Opposition took the form of letter-writing campaigns. In January 1990, Leslie Kozak, from the Jackson Laboratory in Maine, sent a letter to Senator William Cohen stating that the genome project "threatened the quality and conduct of our nation's health-related research effort."[50] In February, Martin Rechsteiner of the University of Utah wrote letters to acting NIH director William Raub, presidential science adviser D. Allan Bromley, and Senators Al Gore and Ted Kennedy. The letter began: "The human genome project is mediocre science and terrible science policy."[51] Rechsteiner's letter questioned the origins of the project in DOE, warned of sequencing drudgery, challenged the value of sequencing the human genome, and urged that the project be curtailed to reduce divisiveness within biology. Thus began a string of letters, some of which included copies of the Rechsteiner letter, indicative of a concerted campaign against the genome project. *Science* and other periodicals got wind of the campaign and reported that Rechsteiner had sent his letter to five hundred scientists.[52;53] Rechsteiner cited Bruce Alberts's *Cell* editorial warning against Big Science in biology, apparently unaware that Alberts had chaired the NRC panel that crafted the genome strategy.

A series of other letters began to pass through the electronic mail networks in biology. One such letter by Michael Syvanen (University of California, Davis) and his colleagues urged that scientists write to their own congressional representatives to kill the genome project.[47;52;54] Robert Martin, an intramural NIH researcher, expressed concern that the genome project was overly concentrating research funds and would misdirect biology.[55] Even in peer review meetings for genome grants and on-site visits to prospective genome research centers, dissension was palpable among the reviewers. The opposition was critiqued by Dan Davison at Stanford, who observed that the central issue was not the genome project *per se,* but the paucity of investigator-initiated project grants. The genome project was indeed going to be more targeted, and should be more open about it, but the genome budget was but a drop in the bucket,

and killing it would do little to ameliorate the funding squeeze.[56] In June, the *New York Times* juxtaposed features on mounting opposition to the genome project and on the wrenching dilemmas faced by young investigators.[57;58] The dilemma was real, although the genome budget was not the root cause.

In mid-July 1990, the four offices targeted by Rechsteiner indicated they had received thirty or forty letters on the genome project, running four or five to one against it. (By comparison, the Superconducting Super Collider generated about ten times more mail at the White House Office of Science and Technology Policy, in more or less the same ratio.) When genome supporters got wind of the campaign, they reacted with letters of their own, so that by mid-August the odds were evening up.[59–62] Each of these four offices read the opposition primarily as a reflection of self-interested group politics. Congress and executive agencies were hearing strong support from the clinical genetics community, which wanted rapid progress on human genetic disease, and from industry.

The Industrial Biotechnology Association (IBA) did a survey of its member companies in fall 1987 and found strong support as long as the project was conducted by NIH.[63] At the IBA annual meeting in May 1988, Patrick Gage (then of Hoffmann–La Roche) waxed rhapsodic about the genome project in a talk titled "Why We Should Do It—Now!"[64] Two other respected leaders of pharmaceutical research and development teams, George Poste (Smith, Kline & French) and Ralph E. Christoffersen (then at Upjohn), were equally upbeat at an October 1987 meeting of the Pharmaceutical Manufacturers' Association.[65] When the University of California at Los Angeles did a survey, principally among industrial groups interested in the genome project, it found that government and industry figures were much more likely than academic scientists to consider the genome project "a worthwhile use of taxpayers' money and scientific resources." The survey found 62 percent of industrial respondents, 70 percent of the financial community, and 88 percent of those from government agreed, but only a slim majority among academic researchers (thirty-five for to thirty-one against).[66] When the Industrial Research Institute surveyed its member companies about five major science projects—the Superconducting Super Collider, the Hypersonic Airplane, the Strategic Defense Initiative, the Space Station, and the Human Genome Project—the genome project came out on top by a wide margin (with more than twice the votes of the next-nearest project).[67] Industry and government administrators clearly thought the project had promise, at least by comparison to other large science projects. One reason the academic backlash failed to make inroads was its confinement to academic circles.

Opposition within science peaked with the publication of a commentary from Bernard Davis and his colleagues in the microbiology department at Harvard Medical School, in the July 27, 1990, issue of *Science*.[68] This short article made clear that competition for research funds drove the opposition. Davis saluted the redefinition of the genome project by the NRC, but argued

that "it is doubtful that they [genome projects] could generate the strong political appeal of the original proposal." The letter urged that any sequencing projects be targeted at "units within the chromosomes that have functions." Finally, it hit the center of contention, by asserting that work on model organisms lacked "obvious justification for insulation from competition with other kinds of research," signaling that the real basis for suspicion was that genome research was protected from peer review, or escaped comparison to other research priorities. Given that all genome grants were being channeled through standard NIH peer review, contention centered on whether genome research deserved its own bureaucratic center and how large its pot of gold should be.

Davis agreed that some elements such as databases needed centralized management, but the genome office was getting too big a slice of the biomedical research pie. The letter asked for a reevaluation of the project and questioned whether it deserved funding "at a level equivalent to over 20 percent of all other biomedical research," although the origin of that estimate was not specified. If the source of concern was the 1991 budget, between $60 and $70 million of the $108 million request was uncommitted, amounting to 4 or 5 percent of the funds slated for new and competing grants at NIH that year. Five percent was the figure Davis himself used later in congressional testimony.[69] The Davis letter made clear that 20 percent (or 5 percent) was too high, but 0 was too low. How much was the right amount?

The House appropriations subcommittee was attempting to preserve all it could for investigator-initiated grants, and it cut the 1991 genome budget, but this was not due to the letter-writing campaigns. Subcommittee staff learned of the campaigns only when Watson mentioned them, and when Leslie Roberts of *Science* called to ask if the Rechsteiner and Syvanen campaigns were related to the cuts.[47] The campaigns failed to target members of the appropriations subcommittees in either House, thus violating the first principles of interest group politics. The principle of preserving funding for small grants, even at the expense of other programs, was the motivating force behind the budget cuts, and did the work that those hoping to lobby failed to do.

As the genome project neared its official starting date of October 1, 1990, the curtain rose on a public drama. On July 11, the Senate held a hearing before its Committee on Energy and Natural Resources, chaired by Senator Wendell Ford, with Senator Domenici as the ranking minority member and star prosecutor. The Subcommittee on Energy Research was holding its second set of hearings on the genome, two years after the first. Matthew Murray, a former student in Leroy Hood's laboratory at Caltech, now working at the Lawrence Berkeley Laboratory, was doing a short internship in Domenici's office. The idea for a hearing began as a survey of the DOE genome program. The hearing was one of the first highly public acts for David Galas, the new director of DOE's Office of Health and Environmental Research—successor to Charles DeLisi, who first conceived a federal genome research program.

Galas announced that Lawrence Livermore would become the third designated national laboratory genome center, joining Lawrence Berkeley and Los Alamos in the DOE constellation.[70] He also announced a new DOE plan to map and sequence complementary DNAs, regions known to code for protein.[71] As plans for the hearing progressed, Ben Cooper, staff director for the subcommittee, wanted to let genome critics have a voice. He believed their opposition was largely due to misunderstanding of the budget dynamics, and he wanted to give them a chance to speak and be questioned. Cooper invited Martin Rechsteiner and Bernard Davis to testify.

Watson and Galas opened the hearing, followed by the heads of the three DOE genome centers—Robert Moyzis of Los Alamos, Anthony Carrano of Lawrence Livermore, and Charles Cantor of Lawrence Berkeley. Kirk Raab, CEO of Genentech, spoke of industrial support for the project. Leroy Hood dazzled Domenici with reverential references to technology transfer, speaking from his own experience in developing new instruments and methods.

The hearing began as a showcase for the DOE program, but ended with Davis's summarizing the *Science* letter that questioned the urgency of the genome project and asking for a reevaluation of its funding levels.[68;69] Domenici slammed into Davis with a zeal hearkening back to his past as a lawyer. "As someone who is supposed to know all about the federal budget, I am rarely in a position where I can look at a program and say that it is exciting enough to keep somebody like myself energized while we are trying to reduce the deficit, but I have found one here."[72] There was a carry-over debate in *The Scientist,* with Davis arguing that the genome project was prone to become too bureaucratic, and again attacking the notion of sequencing the entire genome.[73] Leroy Hood retorted that the tasks of molecular biology were inherently repetitive, and that the idea of the genome project was to provide the information, methods, and instruments that would liberate molecular biologists from some of the tedium.[74] Martin Rechsteiner missed the opportunity to greet Domenici's wrath.

Domenici was an important Senate figure in the budget summit meetings to trim the federal deficit. He was among the members of Congress working with President Bush, OMB director Richard Darman, and other senior administration officials to hammer out a two-year budget agreement. A budget summit meeting was scheduled in conflict with the genome hearing time, and the hearing had to be rescheduled. Staff notified the witnesses, but could only leave a message for Rechsteiner, who had already left Utah. Rechsteiner entered the hearing room at noon, two hours before the time he thought it would start, only to find it had just adjourned. I greeted him and ushered him to the front, introducing him to Domenici, who was giving post-hearing press interviews. For Rechsteiner, it was a long trip from Utah; it must have been an even longer trip home.

As the House appropriations subcommittee prepared to mark up its bill for the full committee, a critical step in the budget process, Watson exhorted

other titans of molecular biology to write support letters to committee members. I and other staff members feverishly called our contacts to notify them of the genome project's plight. Watson spent days in phone-to-phone combat, turning his considerable energies to shim the sagging fate of his program. The same ardor that assembled the double helix from cardboard and wire models in 1953 constructed the political structures to shore up the NIH genome project in 1990.

In the end, NIH salvaged a livable budget. Representative Obey slashed $36 million from the President's $108 million request in the House,[75;76] but Senator Harkin restored the full request and even added a couple hundred thousand dollars.[77] The final budget was the arithmetic mean, less a few more whiskers shaved off all NIH programs and totaling $89,731,000.[78] The House contingency budget, sequestering genome funds in the NIH director's coffers, was excised. Funding was sufficient to launch six genome centers by February 1991[79;80] and another three by the end of the fiscal year. The centers anchored the strategy sketched out by the NRC committee. Much of the budget remained in investigator-initiated grants, but Watson and his advisers were convinced that data and technologies would come together with sufficient force only if NIH cultivated teams large enough to mount significant interdisciplinary efforts. Letting a thousand flowers bloom would generate marvelous science, but a field of wildflowers could not feed the army of researchers who needed systematic maps and databases.

Those who argued in 1987 and 1988, as many did, that the genome project should proceed only with "new" money came a cropper in 1990. Opponents shattered a fragile argument. If the project was so important, why should it proceed only with "new" money? Was this not just a way of saying it could not compete on its own, and had to be insulated from budget competition? The rhetoric of "new" funding, and the disingenuous argument that genome research would never displace funding from other work, distracted from the central question. Elke Jordan and others argued that the genome project would enlarge the pie by presenting a new objective that Congress could readily support.[53]

The central question remained how much of the NIH budget should go to collective organized efforts, to establish an infrastructure for future genetics, and how much to undirected research and other worthy ends. Initial NIH genome funding in 1988 was just under 2 percent of a budget request increment (or 0.2 percent of the overall NIH budget.). Was Wyngaarden right in his decision to dedicate the funds to genome research? Those who contended that the genome project's budget would displace other science generally argued from an abstract perspective, but there was some evidence to support their position. While the genome project, because of its small size relative to all NIH, had a negligible impact on NIH overall, it did cause some transient "collateral damage" (to borrow a military term) to the basic genetics program at NIGMS.[81–84]

Truth lay on both sides of the "new money" argument. The funding available for investigator-initiated basic genetics grants at NIGMS dropped from $187.8 million in 1989 to $159 million in 1990, before rebounding in 1991 and thereafter. Those same years, the genome budget jumped from $28.2 million (1989) to $59.5 million (1990), the year of maximum adverse impact at NIGMS. The increase in genome budget clearly gave genetics investigators a new place to apply for funds, but the nature of the science was not the same, as it was principally aimed at map construction and technology development rather than undirected analysis of basic genetic mechanisms.

If the genetics program at NIGMS, birthplace of the genome program, had grown at the same rate as other parts of NIH from 1987 through 1992, its budget would have risen to roughly $255 million by 1992. Between the genome research budget and the NIGMS budget, the total was instead $334.4 million, of which $229.5 was at NIGMS and $104.9 was at the genome center. A reasonable conclusion is that the genome project attracted an additional $80 million per year of funding that would not otherwise have been anywhere in the NIH budget while pulling away $25 million that would otherwise have remained at NIGMS. Three-quarters of the genome budget was "new" money appropriated by Congress in response to a new idea, while somewhat less than a fourth was carved out of NIGMS.[85]

The choice facing policymakers was analogous to deciding when a new territory was crowded enough to build roads or make rules about land and water use. When John Wesley Powell surveyed the American West, he realized the central importance of water. He urged a communitarian political solution, one quickly killed by the politics of the day. He lost his position as head of the U.S. Geological Survey, arguably the most powerful scientific position of the time. Senator Walter Stewart, a lawyer from Nevada, deposed Powell through his position on the Appropriations Committee. An ideology of false abundance, including a denial that water was a scarce and controlling factor in the arid regions, doomed the American West to cycles of boom and bust linked to drought and plentiful rain.[86] Powell was a messenger who spoke too soon, before the politics could catch up.

The scarce resource for biomedical research was public dollars, which would also wax and wane. The genome was also largely virgin territory, but molecular biologists had begun to stake claims. When was the time to plan resources for the common good? When should NIH build roads as well as fund more explorations of the vast genetic terrain? The answer hinged on whether the genome project filled an unmet need that if not addressed would exacerbate the scarcity of research dollars.

The NRC committee and leaders of the biomedical research community identified a weakness in the pattern of NIH funding—a neglect of genome-scale mapping efforts, inattention to development of new technologies, and insufficient funding of databases and shared resources. The most senior officials at NIH agreed with that appraisal. How much was it worth to fix the

problems? The strongest argument for the genome project was that in the long run, it would make finding genes faster and cheaper. Finding genes was emerging as a strategic bottleneck in many disparate areas of biomedical research. The genome project was worth doing, and need not have rested on the perilous rhetorical perch of "new" money. An unfortunate choice of semantics failed to acknowledge that the genome project was a response to a policy failure; genetics research had outstripped its support structure. Insisting that genome funding *never* come at the expense of other initiatives belittled its central importance to the future of biology, despite the truth that the bulk of its funds did not come at the expense of research grants. The genome project did cause a several-year downward bump in the NIGMS basic genetics program, although it would be hard to argue that it had a substantial impact elsewhere in NIH.

By the end of 1990, the frustration directed at the genome project had found new targets. The debate continued, but its rancor diminished. The wrath of investigators shifted to the Institute of Medicine (IOM) in late 1990, after it released a report on biomedical research funding. The IOM report concluded that "the allocation policies of the past decade have focused too heavily on short-term problems and solutions and have neglected the long-term integrity of the research enterprise."[44] The committee did three alternative funding scenarios, favoring two growth scenarios: 2 percent or 4 percent per year over inflation. Responding to its charge, however, the committee also analyzed a no-growth scenario. Under that scenario, the committee recommended boosting training and construction funds even if it cut into other programs. This recommendation precipitated a firestorm of criticism among those who feared any incursions into extramural grant funding. (Two years later, however, the strategic planning process at NIH itself had reached many of the same conclusions.)

Animosity about genome research funding also dwindled as more scientists began to appreciate that the goals had been broadened to encompass more than just human genetics, and that it would focus for several years on genetic linkage mapping, physical mapping, and technology development—all consensus goals. Bernard Davis, for one, was mollified.

A rearguard action was fought at the October 1990 Genome II meeting in San Diego. Davis held out an olive branch, telling *Science,* "I don't want to say I have been converted, but there is much less disagreement than there was a year and a half ago."[87] Not to mention four months ago. Michael Syvanen claimed that opposition had not diminished, but his claim rang hollow.[88] Donald Brown from the Carnegie Institution fought against a retreat. He argued that the genome project was "overtargeted, overbudgeted, overprioritized, overadministered, and has to be micromanaged."[87;89] Brown remained at one pole, unconvinced that the genome project should displace funds from project grants. He cited the fact that oncogenes and other major discoveries of the 1980s had flowed from research throughout NIH,[89] much as farmers and

ranchers pointed out in the 1860s that *they* were the producers in the American West.[86] Who was John Wesley Powell to suggest that the West would benefit from planning, especially regarding water use? Communitarian values were invidious, and collective actions antithetical to the prevailing ideology.

In his opening talk at the San Diego meeting, Watson anticipated criticism of DNA sequencing efforts: "Saying that you support mapping without sequencing is like saying I'll marry you but there will be no sex."[87] Vintage Watson. Watson later got into a shouting match with Brown. Walter Gilbert closed the meeting with a call to arms. Biology was undergoing a fundamental change, and genome researchers were the shock troops. "The paradigm of molecular biology that Don Brown and Bernie Davis spoke from was that biology is a purely experimental science. In my mind that paradigm is shifting."[87]

Planned research efforts were new to molecular genetics. Shifting from a set of completely independent project grants to a coherent program with definite goals gave the research community some bumps and bruises. One early controversy about achieving goals erupted over refinement of the genetic linkage map. The NRC report had set the goal of a one-centimorgan map, so that the density of ordered markers along the chromosomes would be spaced an average of one million bases apart—close enough to help orient physical mapping efforts. With a map at this degree of resolution, a gene running in a family would be located with enough precision to go directly to analysis of DNA from the region. At the December 1989 meeting of the NIH program advisory committee, Maynard Olson commented: "There is a zero probability that we will develop a one-centimorgan map unless there is a major change of policy. Is this a goal or not?"[90] David Botstein seconded Olson's concern, and the issue was covered prominently by *Science* and *The Scientist*.[90;91] Five months later, *Science* reported the map was "back on track" following a meeting of genetic linkage mappers just before that year's Cold Spring Harbor genome conference.[92]

The goals of genetic linkage mapping were scaled back to a map two to four times less dense with ordered markers, in large part because physical mapping techniques and PCR had made it seem likely that fewer markers would be needed to assist physical mapping efforts. It was also beginning to seem plausible that physical mapping and regional sequencing might well assist construction of a genetic linkage map as much as the reverse. This possibility was not apparent when the NRC report was issued early in 1988. The genome project had made a course correction.

A second controversy about targeting research broke out over DNA sequencing projects. Even as the budget battle for fiscal year 1991 quieted down, the question of large-scale sequencing remained an active issue. Passionate disagreements centered on whether, when, and how to begin systematically

determining the DNA sequence of large stretches of the human genome. The two policy documents had parted company on whether a complete human genome sequence was an explicit goal. OTA stopped short of endorsing the idea of sequencing the entire genome, at least directly,[93] believing it was still an open scientific question whether it would be desirable to sequence every last region. The long arm of the Y chromosome, for example, seemed likely to contain large expanses bereft of genes. The NRC report was bolder. The committee reviewed the argumentes for and against a dedicated sequencing project, finally judging that "the ultimate goal would be to determine the complete nucleotide sequence of the human genome."[94]

The origins of the genome project were indeed Sinsheimer's, Dulbecco's, and DeLisi's visions of a fully sequenced genome. The Human Genome Project, however, evolved into a program with considerably broader goals. There was little disagreement that there would be much more DNA sequencing in the future, and that methods to perform it faster, cheaper, and more accurately were essential. There was further agreement that sequencing large expanses of model organisms was laudable and would be highly useful—sequencing genomes of the bacterium *Escherichia coli,* the nematode *Caenorhabditis elegans,* and baker's yeast, *Saccharomyces cerevisiae,* began to move forward. In these organisms, genes were tightly packed, investigators could take advantage of a vast array of genetic manipulations to test gene function, and the scale of the effort was a mere order of magnitude or two beyond demonstrated technical capacities. Sequencing projects in these organisms, funded by the NIH program and a massive multicenter collaboration organized under the European Community, pushed forward the technical frontiers and began to produce impressive results by 1992.[95;96]

The wisdom of the National Academy committee's recommendation to fund animal model work also became abundantly clear in a mouse genome project. The mouse project was not directed at chromosomal sequencing, but rather at constructing a useful map of markers for genetic linkage mapping. There were hundreds of inbred strains of mice, and thousands of mutations defined by their effects on development, behavior, and physiological function. A genetic linkage map would greatly expedite the search for genes underlying the traits and would also enable rapid detection and targeting of new mutations. A genome center organized by Eric Lander of the Whitehead Institute in Cambridge, Massachusetts (with collaborators at Rockefeller University, Princeton, and MIT), produced a map that covered almost the entire genome with highly variable markers.[97] A few gaps remained, but the automated technique promised to quickly fill the gaps with new markers.

The project applied a concerted and systematic search for markers to an entire genome and produced an extremely useful map in a matter of a few years. The collaboration was a model of things to come, combining the resources of an NIH-funded genome center, several investigator-initiated grants from NIH and the National Science Foundation, and private funding from

the Markey Charitable Trust.[97] While this was not a sequencing project, its technology was based on the polymerase chain reaction and many steps entailing large amounts of sequencing. While the purpose of the project was more "biological," in that it produced a tool for analysis along the lines of classical genetics, it was highly automated and dramatically expanded the scale of analysis to at least the same degree as other genome projects. It was not exactly what Sinsheimer, Dulbecco, and DeLisi had in mind initially, but it just might prove even better.

When it came to the human genome, however, there was a fixed chasm between those who wanted to sequence regions of known interest and those who argued that it would be more difficult to find out what was important than to sequence the genome and then pick out the juicy bits. Walter Gilbert long espoused the view that sifting through the genome and deciding what to sequence would be less efficient than sequencing it and using the information to guide biology. Many others argued that sequencing should be restricted to genes and regions of known interest, at least to regions with many genes and densely packed information, until the technology made sequencing considerably less costly.

The sequencing task would be formidable, regardless of which DNA fragments were first selected. Bart Barrell, who had managed several of the world's largest sequencing projects to date at the MRC Laboratory of Molecular Biology in Cambridge, injected a sober note, testing the reality of 1990 sequencing rates against those projected in 1985 by the Santa Cruz position paper. The Santa Cruz group had speculated that sequencing rates of fifty thousand base pairs per week might be feasible by 1988. Barrell shattered this optimism; he estimated that in 1990 the average rate in most laboratories was no more than fifty thousand base pairs *per year*. Barrell pleaded for "a prime goal . . . to make the existing technology more efficient both by making the methodology simpler and more automated and by better strategies that narrow the gap between the theoretical sequencing rate and the practical sequencing rate."[98]

The genome offices at NIH and DOE basically adopted Barrell's commonsense suggestion, which temporized, delaying a commitment to sequencing the entire genome until better technologies were in hand. NIH and DOE sponsored grants to develop entirely new sequencing methods, to sequence the genomes of organisms with densely packed genes and well-developed genetics, and to sequence relatively small regions (one or two million base pairs) of the human genome known to be of intense interest. The sensible position was to support different approaches and see which avenue proved most productive. This did not entirely rein in the controversy, as many in the community remained convinced that the genome project harbored an implicit commitment to sequence the entire genome no matter what.

The joint NIH-DOE five-year plan followed the NRC in stating "determination of the complete sequence of human DNA and of the DNA of selected

model organisms" as its third major objective. The specific five-year goals, however, were to mount pilot projects on model organisms, to reduce sequencing costs to 50 cents per base pair (including preparation and analysis costs), and to sequence ten million bases of contiguous DNA (0.3 percent of the genome).[82] These were hardly utopian goals, or even a Manhattan Project for sequencing.

How to perform large-scale sequencing projects remained controversial. One group favored continued reliance on manual sequencing methods, automating some laboratory steps, but retaining a legion of human DNA sequence readers. A University of Wisconsin project to sequence the *E. coli* genome, directed by Fred Blattner, was the largest effort along these lines. He proposed to sequence the five million bases in that genome by using robots and a small army of undergraduate and graduate sequence readers. George Church at Harvard Medical School, Ray Gesteland at the University of Utah, David Botstein and Ron Davis at Stanford, and others experimented with an embellishment of the Maxam-Gilbert sequencing method, "multiplex sequencing," that enabled dozens of sequence stretches to be read without running new electrophoretic gels. In essence, this was a way to run twenty to fifty sequencing analyses (of three hundred or so base pairs) at a time in parallel. The multiplex method could also be automated, but the automation strategy focused on different components. The complicating factor here was how accurate the sequence determinations would be, and how to meld sequence data from the thousands of experiments into DNA sequence information for long contiguous stretches of chromosomal DNA. One major problem was how to reduce the amount of time humans had to spend fitting the data together. This approach confronted a daunting task of automated image analysis, and another task in detecting DNA sequence matches.

Other groups were committed to pushing the emerging automated DNA-sequencing machines to their limits. Groups at Caltech, Baylor, the National Institute of Neurological Disorders and Stroke (NINDS), and elsewhere mounted large-scale sequencing efforts that relied primarily on DNA sequencing instruments rather than manual sequencing methods. A group at Baylor, directed by C. Thomas Caskey, sequenced a part of the X chromosome containing the *hprt* gene, whose mutant form caused a terrible disease of self-mutilation among boys called Lesch-Nyhan syndrome. The ALF sequenator pioneered by the European Molecular Biology Laboratory, and modified for commercial sale by LKB-Pharmacia, played the central role in this effort.[99] The Caltech group concentrated on sequencing regions of the genome involved in regulating immune functions in both mouse and man. The group at NINDS was madly sequencing regions surrounding the neurofibromatosis region of chromosome 17, the tip of chromosome 4 (in search of the Huntington's disease locus), and regions that contained receptor genes for neurotransmitter receptors—proteins involved in nerve cell and muscle communication.[100; 101] This group then turned to sequencing short stretches of

DNA known to code for proteins,[102] and ultimately a split from NIH under private corporate sponsorship.[103; 104]

The Caltech and NINDS groups employed the Applied Biosystems sequencing instrument as their main sequencing tool. Other groups used these machines to generate the first wave of data and supplemented them with the ALF machine for those sequencing runs that started from specified sequences.[96; 101] By running a series of machines in parallel, massive amounts of sequence data could be generated. The reagents were expensive, and these techniques also required detecting sequence matches and reassembling thousands of short stretches of DNA sequence information into long contiguous sequences.

Walter Gilbert suggested a novel means of extending his and George Church's methods to directly determine DNA sequence data from chromosomal DNA, and he proposed to test the idea on the smallest free-living organism, *Mycoplasma capricolum,* a bacterium that infected goats. William Studier of Brookhaven National Laboratory proposed to use yet another approach to DNA sequencing that relied heavily on both automated DNA sequencers and also automated instruments to generate short stretches of synthetic DNA. Bruce Roe of Brookhaven had early success testing this idea out.

Entirely new approaches to sequencing also began to surface. Several groups—one surrounding Lloyd Smith at the University of Wisconsin, another at a startup firm named Genomyx in the San Francisco Bay area, and yet another involving a collaboration between the University of Utah and the University of Alberta—focused on using small capillary tubes and highly sensitive detection methods. If successful, these would dramatically reduce the amount of DNA needed for analysis and at the same time increase the speed of sequencing a hundredfold or more. Exotic methods were tested as well, in the various national laboratories and small pilot projects supported by DOE and NIH. One method hoped to apply direct analysis of individual DNA molecules through scanning-tunneling electron microscopy; another chipped one nucleotide at a time off a DNA molecule and would require new technology to detect a single labeled molecule.

These contesting methods were hotly debated among sequencing wizards. J. Craig Venter, C. Thomas Caskey, and Jack McConnell convened the first DNA Sequencing Conference at WolfTrap, in the Virginia suburbs surrounding Washington, D.C. This conference took place in October 1989 and included a gala reception at the Phillips Collection near DuPont Circle in the District of Columbia. Sequencing enthusiasts saw this conference as the one that put large-scale sequencing on the map. Sydney Brenner closed the session, noting that "most individuals involved in the genome project had effectively written off the initiation of large-scale DNA sequencing for at least five or more years. This conference has clearly moved DNA sequencing to the forefront of the genome effort."[105] Those committed to use of automated DNA sequenators took the meeting as a vindication, a turning point in the genome project.[106]

Craig Venter and C. Thomas Caskey organized the second DNA Sequencing Conference in Hilton Head, South Carolina, a year later.[101] It began on October 1, 1990, Watson's decreed starting date for the genome project as a whole. Watson affirmed the importance of sequencing and directed his plea to the sequencing enthusiasts. He forcibly noted that rhetoric had sustained the DNA sequencing promoters for several years. It was time to produce mountains of data, and let the usefulness of DNA sequence information prove itself to the skeptics. He believed sequencing data from some projects—*Escherichia coli* and *Saccharomyces cerevesiae*—were so important that they should be pursued as crash projects, even if there was no agreement on one "best" method. Watson asserted that DNA sequencing was the focus of those who contended the genome project was bad science and that Congress had made a mistake in funding it. The earliest proposals for DNA sequencing were "shouted down" by the sequencing experts themselves in review committees. The community was highly fractious and opinionated, to the detriment of the field. Those interested in demonstrating the effectiveness of DNA sequencing as a scientific strategy would do better to convince skeptics by overwhelming them with important results rather than continuing to talk vaguely about the promise of sequencing.

Watson also noted the need for a common policy on the release of sequence data. He personally favored release of data as soon as investigators were confident about accuracy. The criteria for accuracy were unclear, however, as was the relevance of sequence data to proprietary uses (e.g., for commercial diagnostic tests or as data important to secure patents). Those doing large-scale DNA sequencing had to discuss criteria for data release as a first step toward consistent policies. Watson sought answers about these questions because he felt certain Congress would want to know who would have access to sequence data and when data would be deposited in public databases.

Watson's impact was felt far outside the Washington Beltway, the ring that marks off that part of the nation whose main preoccupation is the federal budget process. He had perhaps his greatest impact establishing the long-term scientific strategies of the genome project in its critical opening phase. One measure of his success was the quality of the investigators he brought into the fold. Genome centers and large genome grants established in the first wave of NIH funding were directed by scientists of supremely high caliber. Many were candidates for Nobel Prizes or thought likely to achieve that stature in the coming decade: David Botstein and Ronald Davis (Stanford), C. Thomas Caskey (Baylor), Francis Collins (Michigan), Glen Evans (Salk), Eric Lander (Whitehead Institute), Rick Myers and David Cox (University of California, San Francisco), Ray White and Ray Gesteland (Utah), and Walter Gilbert (Harvard).

Another administrator might have secured the same budget, but none could similarly create the ambience of "hot" science. If molecular biologists were sharks cruising the seas in hunt of tasty morsels, Watson was a great

white. Norton Zinder, chairman of the NIH program's advisory committee, commented that "the spring of 1988 saw a quantum leap in the program's credibility" when Watson agreed to serve.[107] Watson took away one of the strongest arguments offered by genome critics—with Watson at the helm, it was difficult to argue that the science was mediocre. Watson had the trust of those who were initially skeptical of the genome project. Botstein commented on Watson's strong sense of priorities in the genome project: "We need to test its progress, regulate its growth, and slap it down if it becomes a monster. Jim Watson understands the dangers as well as any of us."[108]

Watson trudged through the muddy battlefield of genome politics in 1990. In early 1991, the genome project achieved its first direct presidential endorsement, along with a request for $110.5 million in the presidential budget. (DOE had requested $59 million.) In his remarks to the National Academy of Science in April 1990, and again at the American Association for the Advancement of Science in February 1991, President Bush saluted small science, but also gave explicit commitments to the genome project, high-speed computing, and a global change science program.[109;110]

Watson shepherded the genome project at significant personal cost. The project needed him far more than he needed it. In this regard, Luria's biting comment, aimed at Watson in a thinly veiled reference to "power-seeking enthusiasts," was especially wide of the mark.[49] Watson did gain power, but he lost any semblance of normal life. He had long been famous, but the genome project dramatically increased press requests and solicitations for articles. There were more profiles to add to his already well-stuffed files. The travel schedule was brutal for a man in his mid-sixties, and much of the attention was intrusive and unpleasant. Robert Wright pilloried Watson in *The New Republic*. Watson's photo graced the front cover under a question in large, boldface type: "Mad Scientist?"[111] The public criticism stung, however little Watson cared to admit it. He said he could take the heat, but this was hardly fun.

Watson did not direct the NIH genome program for fame. It was the attraction of power, but not so much power over people as power over the future of science. The project seemed important to the future of biology, and Watson wanted it done right. That sense of duty extracted a commitment from him. It was clear the pressure and attention wore Watson down; at times he seemed almost resentful. Had he sensed there was another person able to carry the ball so far and so fast, he would have handed it off gladly.

Every public statement he made was taken as a policy proclamation. This was a particularly onerous adjustment for Watson, who was accustomed to a smaller and more local power base, where his outbursts washed away quickly and his personality was simply accepted as part of the Cold Spring Harbor firmament. Watson had to learn to restrain his characteristic strong-minded statements about what should be done, because his incomplete thoughts and trial balloons became instantly associated with NIH policy. He could restrain

his impulses, but not obliterate them. He still made a much more colorful director than most. Like senators, members of Congress, and other public figures, Watson learned the confinement of power. He did not relish his temporal power over others, and he resented its intrusion into his personal life. He was, therefore, a great if reluctant leader.

Like Powell before him, Watson fell afoul of policy decisions by those more powerful. He resigned in April 1992, after a long-standing disagreement with his boss, NIH director Bernadine Healy. His stint as director of the NIH genome center was already drawing to an end, and he said as much in January 1992 at a genome advisory committee meeting. His exit was accelerated by a controversy over the patenting of DNA sequences that began in the summer of 1991. Before we turn to the Watson exodus, however, the international and domestic political stage must be set.

PART FOUR

Genome Gone Global

14

First Stirrings Abroad

THE GENOME DEBATE that began in the United States quickly spilled across national borders. The international ethos of science had little regard for political boundaries. As scientists in many nations approached their governments to seek funds for new genome research programs, many met with success. The first success was Charles DeLisi's program in the U.S. Department of Energy. The next was in Italy.

Italy's genome project began as a pilot project in 1987, under the Italian National Research Council, less than a year after the first DOE reprogramming began in the United States. The Italian genome program traced its origins to Renato Dulbecco's 1985 Columbus Day lecture in Washington, D.C., in which he first unveiled his idea of sequencing the human genome as the next major step in cancer research.[1] Consensus formed around Dulbecco's subsequent *Science* editorial,[2] and a program was quickly formulated and ratified by the Italian government. It was announced in May 1987 by the National Research Council.[3] Italy saw genome research as a road to world stature in molecular genetics. Dulbecco was appointed the project coordinator, with Paolo Vezzoni as the deputy, and the project grew from fifteen participating groups initially to twenty-nine by 1989.[4] The budget for the Italian program was $1.25 million for each of the first three years.

Dulbecco explained that "from the beginning, the project was organized on the concept that it would be carried out by many units scattered throughout

the country, because none of the units had all the necessary skill and equipment. To give unity to the project, a common objective was selected: [the end of the long arm of] the X chromosome (Xq 28-Xq ter). Representatives of the various units [met] two or three times a year. This approach led to active collaboration among units. Collaborations also developed with various laboratories in Europe and the United States."[5]

The next national program emerged in the United Kingdom. The program there was deeply rooted in the history of molecular biology. British science was intimately woven into the fabric of molecular genetics. Indeed, the need for a specific genome research program was less acute in the UK, since research very much along the lines of the genome project was philosophically in line with long traditions of British science. The Medical Research Council (MRC) Laboratory of Molecular Biology in Cambridge honed the cutting edge of DNA sequencing and physical mapping technologies and remained one of the world centers for molecular biology, with or without the genome project. On the other hand, the laboratory's traditions fostered the rapid emergence of the genome project, and so while it may not have been needed to the same degree as elsewhere, the genome project was a natural extension.

Representatives from the MRC laboratory in Cambridge attended the major genome meetings in the United States, beginning with John Sulston's presence at the first genome-specific meeting in Santa Cruz. British scientists' views were almost automatically solicited because molecular genetics there was a major part of the science, and there was only one world science. Wherever one looked at molecular biology, scientists from the UK were engaged in audacious projects to push the limits of structural biology. Two figures loomed especially large in the UK.

Walter Bodmer and Sydney Brenner were immediately in the fray as the genome debate began. Bodmer directed the the Imperial Cancer Research Fund (ICRF) in London, a privately funded research center with an international reputation, particularly in genetic aspects of cancer and other diseases. He was known throughout the world for his work on genetic variations in the immune system and in cancer, and on human population genetics,[6–12] and he was chosen by Watson to keynote the Cold Spring Harbor meeting on human molecular biology in June 1986.[8] He also chaired the HHMI meeting in Bethesda two months later. Sydney Brenner from the MRC lab attended several early meetings and was later invited onto the National Academy of Sciences committee. Brenner and Bodmer were positioned close to the centers of power in science in the UK and served as British ambassadors to the larger world of molecular biology. Brenner was highly positioned in the MRC, holding several different posts while the genome debate was underway.

The British genome debate began in 1986, when Brenner suggested to the MRC that he start a Molecular Genetics Unit that would include genome research. Brenner jump-started the UK genome program with funds from a

private £300,000 ($525,000) award he received from the Louis Jeantet Foundation.[13] He proposed to apply the physical mapping methods developed for *Caenorhabditis elegans,* pioneered by John Sulston and Alan Coulson of the MRC laboratory in Cambridge, to the human genome.[14]

Brenner thus drew MRC directly into genome planning. At Brenner's request, MRC established a scientific advisory board, chaired jointly Sir James Cowan, as secretary of the MRC, and Bodmer, as director of the ICRF. Membership reflected the interests of other research councils and private charities. ICRF and MRC were expected to contribute roughly equal funding, and coordination was via a joint scientific advisory committee. In February 1989, the secretary of state for education and science announced that £11 million would be provided to the MRC over three years.[15;16] The UK genome program officially began in April 1989 as a three-year project, but expected to attain a stable annual budget of £4.5 million beginning in 1992.[15;17]

The scientific strategy was a two-pronged approach. One prong was to coordinate ongoing work, including databases and material exchange centers; the second prong was intended to goad basic genome research with additional funds and ambitious technical aims. The approach to international coordination was, in essence, "Let's get started and then we'll talk." Brenner noted that once "we have established a center in the UK which has already been of value to our research community, then we will be well placed to play an active role in international efforts."[16]

During its first year, the UK program focused on automation, new techniques, and mapping regions of special interest. It then shifted to focus on cloning, mapping, and a stronger emphasis on protein-coding regions.[18;19] The genome program included work on mice, especially a mapping effort based on cell lines taken from back-crosses between two species of mice that enabled straightforward physical mapping. Work on *C. elegans,* of course, remained a prominent feature of British genome research. The UK effort was subsequently focused even more on protein-coding regions of the human genome and informatics. The program imported the yeast artificial chromosome library developed at Washington University in St. Louis, to make the clone set available in Europe. It collected a set of DNA probes at ICRF and increased access to human cell lines stored in a repository at Porton.[20] Access to the Genome Database at Johns Hopkins was acquired in 1991, making the UK the first node outside Baltimore.

Progress was recorded in a newsletter that disseminated information about resources, ongoing projects, program plans, new techniques, and summaries of major meetings. Carrying on a long tradition of British humor, the first three issues were named the *G-String.*[21–23] (This name, of course, referred to a DNA sequence of guanines.) The title was then changed to *G-Nome News*[24–27] Early issues focused on the UK, but later editions broadened to cover other countries in Europe. Tony Vickers was appointed human genome mapping

project manager in 1990,[24] and the Human Genome Resource Center was established at Northwick Park, Harrow, later that year.[25] Vickers remained director until late 1992, when Keith Gibson took the reins.

One novel element of the UK effort was a transatlantic bridge built on the nematode work. The *C. elegans* physical mapping effort, one of the prototype projects for physical mapping, grew into a U.S.–UK collaboration to sequence the genome.[28] The nematode was once again to serve as the pioneer for a new technological feat. Brenner's chosen organism was yet again to push back the frontiers of biology. The *C. elegans* collaboration was so successful that it became the backbone of a major expansion of genome research efforts in the UK during 1993, which included John Sulston becoming the director of genome research at a newly founded Sanger Centre funded by the MRC and the Wellcome Trust, at facilities in Hinxton Park, south of Cambridge (see Chapter 20).

During the first two years of the genome project, attention in the UK turned to hosting the eleventh Human Gene Mapping Workshop (HGM 11) in London, with the ICRF as host. UK scientists came to feature prominently in international genome politics, far beyond the budgets supporting their work. Bodmer replaced Victor McKusick as president of HUGO in December 1989. He gave a presentation to the Parliamentary and Scientific Committee, a science policy forum, to bolster support for genome research.[29] Malcolm Ferguson-Smith of Cambridge became chairman of the European Community working party to formulate the EC genome analysis program.[19] Brenner, one of the Nobel committee's more conspicuous oversights, remained a major scientific force. Work on *C. elegans,* pioneered in the UK, continued to serve as a prototype for human genome research.

Even as plans hatched in Italy and the United Kingdom, a genome project of a different character was beginning in the USSR. The project there took root in scientifically rich but politically unpromising soil, and by the time it reached full flower, the USSR was the former Soviet Union and science was struggling for its very life in hard economic times.

The instigator of the Soviet program was Alexander Alexandrovich Bayev, who survived the Gulag from 1937 to 1954 and in old age weathered the many government transitions of the late 1980s. In the far north, he was known for having built a hospital for children in Norilsk. He was sent there in exile, having survived a term in one of the most brutal prisons in the Gulag. Bayev met his second wife in Norilsk (his first wife divorced him after he went to prison). The same perseverance and vision that created a pediatric hospital during the 1940s led in 1988 to the creation of the world's third national genome program.

Bayev's irregular life story is but one of millions—the legacy of Stalin's destructive repression. Bayev trained as a biologist and had obvious talent as a young man, but his career was interrupted during its most productive phase,

from age thirty-three to fifty, by imprisonment and exile. Bayev was born in 1904 in Chita, east of Lake Baikal and north of Mongolia. He studied mathematics and physics and later transferred to medicine, graduating in 1927. He decided to pursue a research career. In 1930, he became a graduate student under Vladimir Alexandrovich Englehardt in Moscow.[30] Bayev's trouble began in 1937, in purges against those who might possibly be supporters of Stalin's rivals Bukharin and Trotsky.[31] These purges directly caused the death of millions, rent the social fabric of the Soviet Union, and hurled Bayev to the outer reaches of Russia.

Bayev was sent to Solovetskiy Special Prison, an infamous detention center on an island in the White Sea. He was then exiled to Norilsk, where he survived by reverting to his role as physician.[30] In the frozen north, Bayev was connected to the outside world only through his mother, who soon died. He remained entirely isolated for several years, not wanting to endanger friends by writing to them. In a brief political thaw during 1944, Englehardt got a letter to Bayev inviting him to Moscow. Bayev ventured to Moscow, working out of Englehardt's apartment because he was unable to visit libraries. Bayev returned after a few months to Norilsk, leaving behind a dissertation on molecular biology that culminated in "candidate of science" status. He was briefly freed in 1947, but arrested again and sentenced to exile "forever." Forever lasted until 1954, less than a year after Stalin's death. Englehardt managed to retrieve Bayev when a period of enlightenment somehow held the Soviet bureaucracy at bay for a year or two. Bayev resumed his scientific career in Moscow, first at the Institute of Biochemistry and later at the Institute of Molecular Biology.[30]

Bayev missed out on the beginning of the revolution in biology taking place in the 1950s. He was in exile when Watson and Crick published their structure of DNA. The USSR contained few scientists able to appreciate the achievements of molecular biology. T. D. Lysenko exercised a vigorous ideological aversion to genetics and made sure others shared his enormous blind spot. Lysenko killed the field by repressing its practitioners, turning Soviet genetics into a wasteland populated only by those few brave souls willing to bet that times would change, or too tough to care. For two decades, genetics and molecular biology were systematically suppressed.[32;33] After Stalin's death, Lysenko slowly began to lose his lock on biology and agriculture. Bayev's mentor Englehardt was in the vanguard opposing Lysenko; as a consequence, Englehardt temporarily lost his position in the section of biology of the USSR Academy of Sciences in 1958. Lysenko was almost deposed in 1959, as an Academy of Sciences committee was poised to censure him. The committee was thwarted the evening before its report was to be made official, when Nikita Khrushchev rescued Lysenko.[33;34]

Englehardt persevered. In 1962, he presented a paper to the Academy of Science asserting, against the Lysenko ideology, that the recent accomplishments of molecular biology were not flukes, but the first fruits of a scientific

revolution.[33] In June 1964, Englehardt worked to block appointment of a Lysenkoist to the Academy of Sciences. He was supported in his efforts by Andrei Sakharov.[33] Sakharov's prestige, derived from physics and thus independent of Lysenko's power base, was essential to the effort. Indeed, it was Sakharov's struggle against Lysenko that first gave Sakharov fame as a political actor, with an impact well beyond his scientific field.[35]

Khrushchev reacted sharply to Englehardt's brashness, calling for an investigation of the Institute for Physical Chemistry and Radiation Biology, where Englehardt worked, but the academy stood behind Englehardt, failing to admit Lysenko's colleague. Englehardt and others ultimately prevailed; Lysenko was finally debunked publicly later that year.

Englehardt became director of the Institute of Molecular Biology and brought Bayev to work there. A young student working for Bayev, Andrei Mirzabekov, was attaining recognition as a rising star. Mirzabekov was born the year Bayev was arrested, in 1937. His family moved to Moscow in 1943, and he became interested in biology. In 1971, Mirzabekov was permitted to go to the West. Mirzabekov went to the MRC laboratory in Cambridge, where he worked to crystallize transfer RNAs for analysis by X-ray crystallography, a technique used to study the three-dimensional structure of DNA and proteins. He managed to extend his stay for six months through the machinations of Aaron Klug, Francis Crick, Frederick Sanger, and Max Perutz (all Nobel laureates).

Mirzabekov was a link between the USSR and world molecular biology in the mid-1970s. He felt the full force of molecular biology from its epicenter, at the MRC laboratory in Cambridge. Mirzabekov returned to the West in time to participate in several major events. He attended the 1975 Asilomar meeting about the safety of recombinant DNA. While in the United States early in 1975, Mirzabekov had a famous lunch with Walter Gilbert, Allan Maxam, and Jay Gralla at Harvard, related to what later became a technique for DNA sequencing. Mirzabekov discovered that DNA could be destabilized at specific base residues by dimethyl sulfoxide, adding methyl groups to guanine and adenine, and causing the DNA to fragment at positions containing those bases. Gilbert and Maxam used Mirzabekov's chemical modification methods to study the binding of protein to DNA[36] and extended the method into the Maxam-Gilbert DNA sequencing method.[37] (See Chapter 4.)

Through the 1970s and 1980s, Mirzabekov and Bayev continued to work at the Institute of Molecular Biology in Moscow, now called the Englehardt Institute. (By tradition, institutes of the USSR Academy of Sciences were named for their founders several years after their death.) They and others in Moscow and Leningrad brought new approaches to Soviet biology, adopting recombinant DNA research and the other new techniques. In 1986, at age eighty-two, Bayev declined to become director of the Englehardt Institute. He recommended Mirzabekov for the job, and Mirzabekov became director that year.

Mirzabekov remained active in science, although his time was increasingly devoted to administrative duties and politics necessary to preserve the health of the Englehardt Institute. Several Soviet scientists were particularly interested in developing techniques for DNA sequencing that might be less demanding of reagents and robotics, commodities hard to find in the Soviet Union. Less reliance on high technology and Western reagents made the likelihood of a Soviet contribution to the sequencing effort more feasible. His laboratory continued to analyze protein-DNA binding. Hans Lehrach of the Imperial Cancer Research Fund in London suggested a DNA sequencing technique based on binding very short segments of known sequence, in the range of eight or more base pairs in length, and determining whether these bound specifically to a given DNA fragment. If they bound, then that sequence was present on the DNA fragment. By binding a large number of such short segments and identifying which short sequence stretches were present, the sequence of the fragment could theoretically be determined. There were several difficult technical obstacles for such a method. A positive score, when bases of the short segment exactly matched a sequence on the fragment to be sequenced, for example, had to be reliably distinguished from a negative, if the match was inexact. Moreover, for the method to be practical, thousands, perhaps even hundreds of thousands, of the short DNA sequences had to be tested and scored at once, despite subtle differences in the strength of DNA binding for each short segment. The potential advantages in speed and simplicity once a system was set up, however, made this sequencing scheme tantalizing. Mirzabekov's group worked to make it a sequencing method, as did a Yugoslav group under R. Drmanac and R. Crkvenjakov[38;39] and groups in London and the United States.

Bayev and Mirzabekov became the champions of the USSR genome program. Bayev learned about the genome project from Walter Gilbert and James Watson, during a visit to the United States in 1986. Mirzabekov attended the 1986 symposium "The Molecular Biology of Homo sapiens" at Cold Spring Harbor that same June. Once back in the USSR, Bayev and Mirzabekov worked to build support for a Soviet genome program.[40–47] Their timing was propitious, capturing the initiative at a time of great change under Mikhail Gorbachev.

The genome project benefited from the new policies of *glasnost* and *perestroika*. *Glasnost,* openness, made it possible to acknowledge, at long last, the damage Lysenko had wrought on genetics and molecular biology, and to begin repairs. *Perestroika,* restructuring, as applied to biology, sought to link science and biotechnology to national economic goals. A first step was to bring Soviet molecular biology up to world standards. The Soviets renewed attention to peer review and other aspects of science funding and science administration.[48] Bayev and Mirzabekov wrote to their colleagues to build support for a USSR genome program, intended to match the movement gathering force in the United States. Bayev argued that "there are times in the history of science

when far-reaching decisions must be made, and in the field of molecular science, one such moment is upon us."[49] The genome project met opposition, principally based on its importance relative to that of other areas of science, in 1987 and again in February 1988, when Bayev made a presentation to the general assembly of the USSR Academy of Sciences. Bayev and Mirzabekov persisted, however, and eventually brought their colleagues and political patrons around. A program was presented to the Council of Ministers in 1988. It was approved, and in 1989 the State Committee for Science and Technology listed it as one of fourteen priority areas in science.[44–47;49–51] Genetics was becoming central to several other initiatives in biology and agriculture as the shadow of Lysenko inexorably shrank in the bright sunlight of modern biology.

The Soviet genome program thus became an instance of *perestroika*. Funds under the project were distributed partially through traditional mechanisms, controlled by the directors of national institutes and laboratory directors within the institutes. Another, more innovative part of the budget was modeled on the NIH project-specific grant system. Mirzabekov, as director of the Soviet genome program, eagerly sought information about peer review and grant administration from his Western colleagues, hoping to reinvigorate Soviet molecular biology by applying Western methods of science administration. The NIH was seen as the most successful agency in cultivating and sustaining molecular biology in the world, and Mirzabekov wanted to bring its peer-review methods, with appropriate modifications, into the USSR.

The budget for the Soviet genome program grew despite hard times for the Soviet economy. The 1988 budget of 25 million rubles was increased to 32 million in 1989. The fax line from the Englehardt Institute to the West exemplified the high priority of genome research, requiring a direct international phone line and a machine purchased with scarce foreign currency. Yet continuing economic turmoil within the Soviet economy imperiled the genome program. Science was caught in the crossfire, in a debate over decentralized planning, and in the tumultuous transition from a centralized communist economy toward a capitalist base. Nevertheless, in 1991, a 40-million-ruble genome program was approved in the national USSR budget.

Many of the institutes of the USSR Academy of Sciences, funded through the central USSR government, were thrown into chaos in the transition from a centralized economy, as the national republics began to wield more political and economic power. The tumult following the failed coup against Mikhail Gorbachev in August 1991 was a period of great uncertainty. With the dissolution of the USSR, the Russian Republic picked up the scientific institutes housing most genome research, but budgets were extremely tight. Science was a relative luxury in an economy reeling out of control after years of central management. Getting food onto tables, building houses, and cultivating other elements of a consumer culture were more important than science.

The genome program was relatively spared during this period of confu-

sion.[52] Indeed, even as science disintegrated through 1992, the genome program was given a line item budget under the Russian Academy of Sciences.[53] This may have been because Bayev and the Englehardt Institute were never closely associated with the political power under the Brezhnev "period of stagnation" and were long associated with reform. Because the genome project was spared, it became the chief vehicle supporting all of molecular biology in the former Soviet Union. Bayev's time in the Gulag and his integrity after returning from it were credentials of great value in the new era.

While attending a scientific meeting in the USSR in June 1989, I visited both the Englehardt Institute in Moscow and the Institute of Cytology in Leningrad (now St. Petersburg). The science at both institutes was seriously constrained by limited infrastructure, but the minds were keen, and ideological constraints were conspicuously absent. The Leningrad institute, in particular, was well populated with erstwhile renegades from the Baltic republics. In hotel rooms where only months earlier the talk would have been hushed for fear of KGB interlopers, there was bold discussion of national politics. Evening discussions became a delightful mix of science and new-wave politics, with predictions of how the central government would dissolve and courageous talk about how that process might be expedited.

Bayev and Mirzabekov presented the genome project as linked to economic development from the beginning. Bayev promised growth through biotechnology in his advocacy for the project. As Russia and the other republics threw off the old order, economic revitalization was the order of the day. The genome project was one of the programs already in place.

Scientists attached to the genome project were all too aware of the daunting task ahead. They were ambitious and bright, but hampered by a legacy of repression. Their work in experimental areas was impeded by limited access to instruments, materials, and technologies from domestic suppliers, and extremely tight budgets for increasingly expensive foreign goods. Regina Eisner, a young molecular biologist from the Englehardt Institute, summarized the prospects for Soviet participation in the genome project: "Soviet science is very good when it does not depend on technology. We have brains and courage. If there are things that need only those, then we can participate."[54]

Bayev embodied the courage and endurance that ran so deep in his culture. He and his fellow scientists had crafted their genome project with an eye to the future. The shape of that future was completely uncertain, but the genome project appeared likely to survive into the new era, a brick in the new edifice.

As genome programs sprang up in Italy, the UK, and the USSR (and its successor political units), parallel developments were taking root elsewhere on the European continent. French genome research began from several centers already deeply involved in human genetics. In 1988, Prime Minister Jacques Chirac announced a FFr 8 million ($1.4 million) program to bolster genetic linkage mapping, to cultivate DNA sequencing, and to foster informatics. Jean

Dausset, director of the Center for the Study of Human Polymorphism (CEPH), chaired a scientific advisory committee to oversee the program.[55] CEPH had long been the collaborative core of genetic linkage mapping in humans. It subsequently expanded its efforts into physical mapping and technology development for sequencing and mapping. Through CEPH and several prominent research groups, France played an important role in the initial genome mapping efforts.

France initially supported selected specific grants in genome mapping, and also to EC programs and the Labimap project for automation (a joint project involving the UK, France, CEPH, and the British company Amersham Ltd.).[20] The early phase of individual grants from French science agencies evolved into a significantly larger and more directed program between 1988 and 1990. Prime Minister Chirac flagged genome research as a national research priority, and by May 1990, the government announced a FFr 8 million ($1.4 million) budget for it, distributed through a committee chaired by Dausset.[56] It was a beginning. The Ministry of Research expressed its intention to mount a more centralized genome research program in June 1990.[57] The ministry charged the National Institute for Health and Medical Research (INSERM) to plan a research program to be formalized later in the year. Philippe Lazar, director of INSERM, delegated the task of formulating plans to Philippe Kourilsky of the Pasteur Institute, who drafted the necessary language. Hubert Curien, the minister of research and technology, formally announced the program on October 17, 1990. The French program was budgeted for FFr 50 million ($8.75 million) in 1991 and FFr 100 million ($17.5 million) in 1992,[58] but 1991 funding actually fell far short of this projection.[59]

A private effort took off faster and produced impressive results quickly. The French muscular dystrophy organization (Association Française contre les Myopathies, or AFM) raised money through telethons and poured the funds into a high-technology approach to human genetics, pursued in conjunction with CEPH. Daniel Cohen, the CEPH director, had worked with Dausset since 1978, and fourteen years later he found himself a leader of French molecular biology.[60] He wowed the crowd of researchers attending the annual genome meeting at Cold Spring Harbor in May 1992, unveiling results on a physical map of chromosome 21 far more advanced than most groups had expected.[61;62]

A collaborating center, the Généthon facility in Evry near Paris, aspired to become the most advanced technological center for human genetics in the world, and seemed likely to achieve that goal, at least for awhile. Between them, CEPH and Généthon employed a staff of 250; the AFM monies provided about 70 percent of the CEPH-Généthon genome budget. Généthon purchased a large number of Apple computers as tools for public education, and a dozen Applied Biosystems automated DNA sequenators.[61;62] Scientists with CEPH produced an impressive stock of yeast artificial clones with great speed and expanded the size of the DNA fragments contained in them through

technical innovations, improving on the other clone collections and thus expediting the direct study of DNA regions in the human genome. When James Watson was asked for his assessment of the best national genome effort outside the United States at the 1993 budget hearings, he responded that "through Généthon, the French have moved to super-production first," and when pressed about which effort was the "number two country," he again replied, "France. Also important are the UK and Japan."[63]

The French genome efforts grew out of a strong tradition of molecular biology. In 1958, when President Charles de Gaulle appointed a committee to look into reorganizing French science, molecular biology emerged as the top priority. Jacques Monod, who shared a Nobel Prize in 1965 with fellow Frenchman François Jacob, chaired a subcommittee that urged the science ministries to foster small problem-oriented units rather than major thematic centers.[64;65]

Jean Dausset's involvement in genome research began with his work on the cellular systems involved in determining tissue compatibility and immune function. An enormously complex family of genes made up the histocompatibility complex. Teasing apart the component genes and proteins took decades. Dausset and his colleagues at the Hôpital St. Louis in Paris were constantly in the fray. Dausset, as leader of the French team, shared a Nobel Prize in 1980 with two U.S. scientists (Baruj Benacerraf and George Snell). An important element of Dausset's work centered on genetic differences among individuals, an essential feature of the histocompatibility complex, and led naturally to an interest in genetic linkage mapping. Dausset took a seed grant in 1983 and brought together the two large groups assembling genetic linkage maps—Ray White's groups in Utah and Helen Donis-Keller's group at Collaborative Research, Inc., near Boston. An art dealer's bequest and partnership with the AFM put the effort on a firm financial foundation,[60] and the science took off. These and other, smaller groups from around the world formed the CEPH collaboration. Paris became a coordination center for producing a human genetic linkage map.

The French genome program grew from several years of discussion, involving INSERM (the National Institute for Health and Medical Research), the National Center for Scientific Research (CNRS), scientists at the Pasteur Institute, CEPH, and several genetics research centers throughout France. Scientists at the Pasteur were less enthused about a massive assault on the human genome.[66] While the private efforts raced ahead, the government program worked its way through the Ministry of Science and Technology.

Genome research, like other research, labored for several years against the rigidities of the French national research system.[58;59] The 1958 commission had not succeeded in freeing molecular biology from the traditional French university system, despite success in nurturing selected groups within it. The private funding through CEPH and Généthon was not so encumbered, and it progressed rapidly. The new government program likewise attempted to re-

move some of the shackles from genome research. It had three major goals—to isolate and sequence protein-coding regions of DNA, to support the complete sequencing of small genomes such as that of *Bacillus subtilis,* and to encourage the development of analytical software. The effort was organized under a quasi-public organization, Groupement d'Intérêt Public (GIP), that enabled the participation of private French firms.[58] The GIP was headed by Jacques Hanoune; François Gros was president, and a scientific advisory committee was to help coordinate efforts and plan strategies.[59] Well into 1992, however, the dedicated genome research program remained a shell without a core of fiscal support. Starved of funds, it teetered. The private Généthon funds, in contrast, were a stable base from which France raced ahead of other nations.

Although Germany had Europe's largest economy, its contributions to human genetics lagged behind those of the United Kingdom and France. It ran a distant third in the number of articles on human genetic mapping, barely edging out Italy and the Netherlands in a bibliometric assessment for 1990.[67] This sustained the pattern that prevailed over the previous decade.[3] Part of the laggardly pace of German genetics was explained by the long shadow of eugenics and racial hygiene in German culture.

The contributions of German scientists to the ideological foundations of the Nazi racial hygiene programs before and during World War II began to be openly discussed in Germany just as the genome project was gaining momentum in other nations. Benno Muller-Hill, a molecular biologist who had worked with Walter Gilbert in the 1960s, wrote an angry book about such "murderous science."[68] His book was merely the first in a a long list of German books about scientists' complicity in Nazi ideology. This ended a long and conspicuous silence. Many of the most forthright racial hygienists from the Nazi era had taken academic jobs in human genetics after the war, and the role of science in Nazi ideology had remained taboo for an entire generation.[69–71] Decades of silence regarding the Nazi activities of researchers lent credence to public suspicions of the academic elite. Many books on the history of eugenics and racial hygiene were also published in English,[70; 72–76] but the cultural sensitivities in Germany were more combustible. What was a subject of interest mainly to historians elsewhere was inflammatory in Germany.

I encountered the difference firsthand in 1989 at a bioethics conference at the Ruhr University, Bochum. I was one of several speakers at a conference on ethics and human genetics at the city outside Düsseldorf. The meeting was almost halted because local students threatened to demonstrate against it. The conference was held, but students were selling booklets alleging that the conference organizer, Hans Martin Sass, was a closet apologist for racial hygiene. I was spared any personal attacks, in part because I was obscure and in part because I was introduced as having worked at the Office of Technology As-

sessment, whose 1983 report on genetic testing in the workplace was lauded several times during the discussion.[77] Although I had little to do with that report (except helping explain RFLP mapping to one of its authors), it nonetheless served to protect me by association. My conversations—with students concerned about the implications of genetics, with clinical geneticists involved in genetic counseling, and with scientists interested in human genetics—made it clear to me that German science would pay a penalty for its long silence. Why would young and able scientists or physicians choose to enter a field so inherently suspect, so widely perceived as tainted in their culture?

The Green movement in Germany was another obstacle to genome research.[14] The Greens had strong suspicions of biotechnology in general and genetic engineering in particular. During the late 1980s, while genome research was first being debated, the Greens were a growing force, and they remained so until caught flatfooted during the 1990 elections, unprepared to deal with the initial enthusiasm for reunification with East Germany. The Greens were concerned at how the results of human genetic research might harm individuals, particularly the use of genetic tests by employers and private insurers. One countervailing force was the AIDS epidemic and the demand it evoked to use molecular genetics to combat a major public health threat. Opposition to genetics had to be tempered by appreciation of its potency in thwarting at least some diseases.

Despite the relative paucity of human genetic research in Germany, scientists there were eager to join in the worldwide genome research effort. Many learned molecular genetics abroad, where it was not subject to the same degree of stigma. They hoped to build a science in Germany that would be seen as a boon to society, rather than a threat. This called for putting genetics on a new moral footing and directly contending with the legacy of racial hygiene.

The German Research Council (DFG) commenced a program centered on human genetics in 1986. In September 1987, representatives of the DFG rejected a position paper prepared by a group of scientists to mount a concerted genome project.[3] Grant funding for individual projects continued, however, under a program named Analysis of the Human Genome by Molecular Biological Methods, which included data analysis and data handling, technology development, basic genetics, and support of European Community programs.[20] This budget was renewed in 1990 for six years at DM 5 million ($2.2 million) per year.[20]

Scientists' other proposals to mount genome programs were rebuffed. A position paper prepared by scientists for the German parliament (Bundestag) died in the Ministry of Research and Technology.[20] A June 1988 meeting in Frankfurt precipitated a consensus that German efforts might concentrate on informatic aspects of genome research, under funding from the Commission of European Communities. This effort led to a three-part program under the German Cancer Institute, for a genome database network node at Heidelberg,

development of a genomic database integrated with the Genome Database at Johns Hopkins, and an initiative to identify open reading frames in DNA sequence data.[20]

The 1990 unification of Germany merged two very different scientific structures. Human genetics in the former German Democratic Republic, or East Germany, had focused by necessity on clinical applications. A program started there in 1986 began to introduce molecular techniques to the diagnosis of the three most common genetic diseases: cystic fibrosis, Duchenne muscular dystrophy, and phenylketonuria. Because of restricted access to Western technologies so necessary to molecular genetic research, scientists in East Germany had little to contribute aside from access to family resources with excellent clinical profiles.[78–80] When the eastern republic joined the western one, it brought a social structure that supported a much higher proportion of scientists. East German scientists were starved but numerous; they had previously been hampered by limited funds to conduct research and limited access to reagents and instruments. Many were now faced with the prospect of unemployment. As 1990 moved into 1991 and the genome program gathered force, the euphoria of reunion gave way to recognition that the two Germanies had indeed drifted far apart in four decades of separation. True unification would be a long process attended with uncomfortable discontinuities on both sides in the early phases. One happy product of this situation was the new Max Delbrück Institute for Molecular Biology in Berlin, at an institute previously part of the East German scientific establishment. One of the founders of molecular biology was thus honored posthumously in the country he fled five decades before, a fitting signal of new directions.

Human genetics in Denmark had a long and distinguished history. Danish medical offices had for many years maintained scrupulous clinical records, and Denmark established repositories containing thousands of cell lines for human genetic research. A special effort had produced a large collection of well-characterized, apparently normal families (i.e., lacking known genetic diseases).[3] Most families were small, although one was large enough to be part of the CEPH family set. Attention to normal families was complemented by a strong capability in clinical genetics. The bulk of genetic illness was referred to a single hospital, the Rigshospitalet in Copenhagen, dramatically simplifying the process of building a genetic registry. While small families were less useful for making a genetic linkage map, the thorough documentation and consistency of clinical assessment were major advantages for hunting down specific disease genes. Danish genome efforts therefore continued the traditional emphasis on clinical genetics.

According to one observer, both the government and the public in Denmark were "more interested in genome research being concerned with disease-related problems than mapping *per se*. Both were content for the United States and Japan to undertake the latter."[20] A genome research center was one of ten

recommended by an international committee of experts in 1989, in evaluating fourteen ongoing biotechnology centers. The Human Genome Research Center at Aarhus University was a reincarnation of the former Bioregulation Research Center that operated from 1987 to 1990. The Genome Research Center commenced work on January 1, 1991, with a mandate to do genetic linkage mapping and physical mapping, to characterize mutations causing human genetic diseases, and to study various functional properties of genes.[20] Its annual budget of 10 to 15 million kronas ($1.8 million) was contingent on government funds from the Medical Research Council being supplemented by the university and other sources.

The Commission of European Communities (EC) hoped to knit genome research in the various EC member states into a coherent whole. The EC program began to emerge early in the genome debate. It grew from a convergence of interests among member states and a desire not to be left in the dust.[19;20;81] Sydney Brenner alerted officers at the commission with a short proposal received February 10, 1986.[82] Further discussions elicited support for projects on *S. cerevesiae, B. subtilis, Drosophila,* and *Arabidopsis thaliana,* and multinational efforts commenced in 1988.[20] These projects were sponsored by various biotechnology programs of the EC. A program on the pig genome was added in 1991.[20] The sequencing of yeast chromosome 3, organized by the EC, was one of the first major triumphs of genome research anywhere in the world.[83] Despite skepticism that a collaboration involving so many laboratories could produce results, the yeast sequencing project nonetheless produced the longest continuous DNA sequence achieved to date. Its progress was undoubtedly slower than it would have been had it been done at a single center, as indicated by the very small amount of sequence data derived from automated methods, and there was ample criticism of delayed access to the data as it was being assembled, but in the end it reached its goal.[84] There was political wisdom behind the choice of a logistically complex collaboration. The widely distributed collaboration avoided a divisive debate over which country would get the political plum, and the support for the project produced by its broad base helped to make it a major success.

Europe promoted several efforts to automate DNA sequencing and to develop other instruments for DNA analysis. The European Molecular Biology Laboratory (EMBL) in Heidelberg received funds from a variety of European governments under a multilateral agreement. In addition to ongoing work in genetics, it also maintained the European node of the DNA sequence database, shared initially with GenBank in the United States. (In 1987, the DNA Database of Japan was also brought in.) EMBL was also the center of an effort to develop a fluorescence-based automated DNA sequencing instrument. EMBL scientists developed a prototype that was later modified and marketed by the Swedish firm LKB-Pharmacia as ALF. Several EC programs focused on biotechnology instrumentation, including the Labimap project

and a joint effort between the University of Manchester and the University of Konstanz. The EC quickly found agreement that informatics and computer analysis of genetic data were important targets not only for genome research, but for biotechnology more generally. The need for data exchange across borders was readily apparent, and agreement on the importance of informatics was readily achieved.

The EC program in human genetics provoked more controversy than studies of other organisms, delaying approval of a human genome program. German research minister Heinz Riesenhuber was a major force promoting EC involvement in biotechnology, including genome research. His interests stemmed from wishing to see cooperative European efforts in biology, but also from the difficulties that research programs in human genetics encountered within Germany. The EC provided a lever to secure support from the German national government for multinational European programs. The EC funds were also an independent pot of funds for which German scientists might apply, entirely avoiding the problems of domestic funding.

Peter Pearson of the Sylvius Laboratories in the Netherlands chaired the working party charged with formulating genome research plans, until he moved to Johns Hopkins University in 1989. Malcolm Ferguson-Smith of Cambridge University then became chairman. The name of the proposal to support an EC human genome program was changed from "Predictive Medicine" to "Human Genome Analysis,[85;86] signaling a recognition of social concerns.[19] The original title had offended German sensibilities, particularly those of Benedikt Härlin, a German Green Party member. Härlin was a member of the European Parliament who served as "reader" for the genome research proposal in its science and technology committee. He sought to ensure that a program to examine the social implications of the research progressed in parallel with the scientific effort.[87] Explicit inclusion of a program to consider the ethical, social, and legal aspects (ESLA) of genome research cleared the way for approval.[88] While the proposal was under consideration, an ESLA working party was appointed, chaired by Martinus F. Niermeijer of Erasmus University, a well-known human geneticist. The ESLA program was allocated 7 percent of the budget, and with the understanding that the genome research program would implement confidentiality protections and would exclude germ line genetic manipulations, it was approved by the council on June 29, 1990.[89]

European efforts to keep abreast of U.S. science spawned several reports in late 1990 and early 1991. The Medical Research Council of the UK was commissioned by Academia Europaea, an organization of academic specialists from a wide variety of disciplines, and the European Science Foundation to survey genome research throughout the world. Diane McLaren, executive secretary of the UK human genome mapping program, did the most exhaustive world survey of genome research to date.[20] This survey fueled conclusions from the ESF and Academia Europaea reports, which agreed in their strategic

conclusions, suggesting that Europe should coordinate its efforts to become a major player in the international arena.

The Academia Europaea report bluntly warned that "there is a need to scale up the contribution of European scientists to human genome research."[90] The ESF report noted that the EC program lacked a single figurehead comparable to James Watson, and concluded, "European efforts appear fragmented, and command individually, fairly insignificant levels of support. . . . There is a danger that the European contribution to genome research may thus be dismissed as insignificant, that European researchers are ignored in the context of international meetings, and that the major players seem to speak for the entire genome community."[67] The reports concurred in their central strategic aims, but differed over tactics.

The ESF report called for stronger central direction and systematic peer review, specifically in the EC program,[67] while the Academia Europaea committee believed "funding for human genome research should remain primarily a national objective."[90] The academic scientists on the Academia Europaea committee recommended a decentralized approach with formation of a new coordinating body (Eurogene) analogous to the task force favored by OTA. ESF favored a bolstering of the EC and ESF multinational institutions to sustain a more coordinated approach. The ESF thus favored cultivation of the existing national research efforts rather than a more tightly coordinated effort. The ESF report got right to the point, arguing that HUGO had failed to articulate its role and pointing to inadequacies in EC program administration.

As 1991 progressed, Bodmer had his hands full organizing the eleventh Human Gene Mapping Workshop and attending to increased financial pressures at the ICRF, which forced him to lay off personnel. The genome project was an opportunity to demonstrate the unity of European science, but the struggle for control revealed the parochial interests of scientists and politicians in the various member states. Lennart Philipson commented candidly in *Nature* on "the animosity and struggle for power within and between the different European organizations involved in funding biological research."[91] Philipson's fervent desire for a coherent but ecumenical planning process for research was widely felt, but the mechanism to achieve it was elusive. It was far easier to specify the end than to devise the means.

In Canada, the genome debate recapitulated debates in Europe and the United States. Canadian genetics was highly esteemed, among the most internationally conspicuous contributions of Canadian science. Canada's genetic services were the envy of their U.S. counterparts, with particularly strong networks in British Columbia, around Toronto, and in Quebec. Charles Scriver of McGill University, who helped involve the Howard Hughes Medical Institute in genome research, tried to work the same magic in Canada. He was not alone. Ronald Worton from Toronto was on HUGO's council and was well

known for his participation in the successful search for the Duchenne muscular dystrophy gene. Canadian geneticists angled for genome funds in the cool waters of distal North America.

In the spring of 1989, interested scientists gathered in Toronto to discuss the possibility of a Canadian genome project. The four meeting organizers (Ford Doolittle, James Friesen, Michael Smith, and Ronald Worton) produced a White Paper, including a long list of supporting scientists.[92] In October, the White Paper was sent to the government and Canada's three main granting councils. The response from Canada's minister for science was swift and positive, but given an austere budget climate, he wanted the granting councils to support the new venture with existing funds. The National Sciences and Engineering Research Council (NSERC) developed a model in which the project would be defined in advance and submitted a large application for funding. In June 1990, the White Paper's authors rejected this monolithic model, favoring an open-ended project like that pursued in the United States. They proposed funding from the Ministry of Science.[93] The Medical Research Council (MRC) agreed to champion this alternative, and the NSERC and the Social Sciences and Humanities Research Council formed an Inter-Council Human Genome Advisory Committee, chaired by Charles Scriver.

In early 1991, the committee recommended "the immediate creation of a genome program in Canada."[94] "Immediate" proved to be a relative term. As the genome project entered its third year in the United States and Italy, Canada's scientists became concerned about their ability to contribute to an international genome effort. As Norton Zinder from Rockefeller University observed, the genome project was "a really exciting global initiative in which Canada is noticeably absent."[95] A summary document prepared for policymakers by Scriver argued:

> Without a Program, in one form or another, Canada: (i) will not long be competitive in medicine, agriculture, the pharmaceutical industry, or biotechnology, etc.; (ii) will not attract or keep the best workers in their fields; (iii) will be marginalized in all life sciences (biology) within the decade. With a Program there will be a sea-change in the way we do life sciences in Canada.[96]

The delayed response from government was only partially bureaucratic. Other factors also contributed, including a severe economic recession and a less elaborate set of connections between science and government. In the end, however, the government flagged genome research as a priority and gave it a fiscal boost.

On June 2, 1992, William Winegard, the minister of science and technology, announced the Canadian genome program at the International Biorecognition Conference. Ronald Worton was named director of a four-year program with $12 million of new funding, a $5 million commitment from the National Cancer Institute, and $5 million from the Medical Research Council.[97] Its goal was to "comprise a coherent, collaborative activity in mapping and sequencing

of genomes, both human and nonhuman; the collection and distribution of data; the training of human resources; the development and transfer of associated technologies; and the evaluation of associated ethical, legal, and social issues." Like its U.S. and European counterparts (except that of the UK), the Canadian program earmarked a fraction of its budget, 7.5 percent, to look at social, legal, and ethical issues. The Pharmaceutical Manufacturers of Canada were expected to supplement this funding, but had made no final decision when the program was announced.[98] The hope was to match the $22 million in government funds, for a total of $42 million over the four years, or just over $10 million per year.[94]

The Canadian genome program thus emerged as a joint effort of three granting councils and the National Cancer Institute of Canada. It was a new independent effort with a management committee chaired by a scientist (Worton) and representation from all four agencies. Peer review committees reported to the management committee, which had the ultimate funding authority. This autonomous program was a departure from the way research was normally funded in Canada, an institutional innovation responding to the need for multidisciplinary research.[93]

As the genome debate become highly public in 1986 and 1987, and as more nations began to hop on the bandwagon, the need for international collaboration became apparent. One of the first responses was to hold international conferences, a natural reflex in the scientific community. The first major international conference on human genome research was organized by Santiago Grisolía of the Institute of Cytology in Valencia, Spain. Grisolía was a biochemist, but he was intrigued by the notion of genome research and fascinated by the cast of characters participating in the debate. In the summer of 1987, he began to organize a lavish conference in Valencia. The idea was initially to invite fifty or so scientists from around the world to discuss mechanisms to promote international collaboration. The conference soon took on a life of its own, as influential scientists from more and more countries, who could not easily be turned away, expressed interest.

The Workshop on International Cooperation for the Human Genome Project took place October 24–26, 1988. The participants were regaled with Spanish high life, including special "genome wine," conference T-shirts, and city buses displaying the conference logo. The workshop proved to be a reality check on what could honestly be expected from mapping and, especially, sequencing efforts.[99] It also revealed a flurry of simultaneous activity in many nations moving toward genome research efforts. Most participants first learned of the Japanese and Soviet genome efforts at this conference. The modest initial French effort and the multicenter yeast mapping and sequencing efforts under the EC were just getting under way. The meeting produced a one-page "Valencia Declaration" encouraging international cooperation, although the precise mechanism provoked a minor controversy.[100; 101] An early draft of the

declaration urged involvement of both the Human Genome Organization (HUGO) and the United Nations Educational, Scientific, and Cultural Organization (UNESCO). Victor McKusick and James Wyngaarden chaired the final plenary session where the declaration was discussed, and the final document emerged with reference only to HUGO.

UNESCO had a new director-general, Federico Mayor, a Spanish biochemist. Mayor wished to renew UNESCO's commitment to science, which had lagged under his predecessor, Amadou-Mahtar M'Bow of Senegal. The United States and United Kingdom left UNESCO in 1984 under M'Bow's reign, strongly objecting to proposed press restraints under a proposed New World Information and Communication Order, but also alleging that UNESCO was an inefficient, expensive, and bloated bureaucracy. Mayor wanted to woo back both countries and saw genome research and other scientific efforts as good opportunities to do so. Scientific efforts were likely to prove less divisive and less purely political than many other programs within UNESCO's purview.

Congress held hearings in April 1989 about whether the United States should rejoin UNESCO. The genome project was mentioned prominently as an opportunity for UNESCO involvement and was listed as the first candidate under life sciences.[102] Mayor visited Washington a year later, in the wake of a State Department statement reiterating opposition to U.S. funding for UNESCO, hoping U.S. policy would change.[103] UNESCO continued to get positive reviews of its reforms, but difficult economic times and emerging isolationist sentiment in the United States undermined support to rejoin UNESCO.[104]

Following a February 1989 meeting of genome advisers from Europe, the United States, Japan, the USSR, and Australia, Mayor appointed a Scientific Coordinating Committee to steer UNESCO's genome program.[105] The UNESCO program began to take shape at meetings in February (Paris) and June 1990 (Moscow). The UNESCO program, budgeted for $260,000 over two years, emphasized training of scientists from countries that would otherwise be unable to participate (from the Third World and Eastern Europe, for example), helping Third World countries to participate directly in genome research, and exploring ethical issues through multicultural exchanges.[106–108] UNESCO contributed funding to several international meetings in 1990 and 1991, notably a high-profile meeting of genome luminaries in Paris, February 1991, and a second conference in Valencia, November 1990, which centered on ethical issues. The centerpiece of the UNESCO program was a short-term fellowship program cosponsored with the Third World Academy of Sciences. This program provided travel funds and stipends for young scientists from the Third World and Eastern Europe to seek training for several months in laboratories in Asia, Europe, and North America. Applications were reviewed just after the November 1990 meeting in Valencia; sixteen fellowships were awarded in the first year of what was to become an annual program.[109] UNESCO also contracted with the Third World Academy of Sciences to produce a directory

of centers interested in or engaged in genome research.[110]

Jorge Allende, an energetic biochemist from Chile, maintained myriad collaborations with scientists in Europe and North America. He shepherded a resolution promoting human genome research through a meeting of the Latin American Network of Biological Sciences in Quito, Ecuador, June 29 to July 1, 1988. The resolution called for developed countries to ensure that the genome project enabled the participation of developing countries, such as those in Latin America. It also urged Latin American governments and scientists to assess local resources and organize into a regional network. The conference participants asked Allende to carry forward his plans for a June 1990 regional workshop on genome research in Santiago, Chile, and asked for partial funding from UNESCO.[111;112] A June 1990 workshop, "Human Molecular Genetics and the Human Genome: Perspectives for Latin America," brought together scientists from twelve countries of Latin America and drew upon scientists from North America. It officially launched the Latin American Human Genome Program.

Allende also edited a special issue of *FASEB Journal* devoted to genome research throughout the world, and described the Latin American efforts to promote training and international collaboration with genome efforts in the technologically advanced countries.[113] It promised to organize into a mechanism for North-South cooperation; the workshop produced another resolution of similar tone and sought continued UNESCO support.[114] UNESCO hoped to see similar regional networks established in Africa, Southeast Asia, and the Middle East.

Populations residing in the Third World were centrally important to understanding human origins and genetic diversity. Consanguinity rates of over 20 percent were not unusual in some regions, particularly where traditional patterns of marriage prevailed under Islam, making recessive genetic diseases more common.[115] Several other religions and local customs encouraged consanguineous marriage. Not only were recessive genes more likely to be detected, but knowledge of consanguinity also presented an opportunity to map genes. The technique relied on the availability of genetic linkage maps to compare chromosome regions from distantly related relatives. If patients with a disease consistently inherited the same chromosomal region, the gene causing the disease was likely to be located there. A gene could thus theoretically be mapped with only a handful of patients, far fewer than needed for more traditional family studies.[116;117]

Large families to enable gene hunting studies were, moreover, often found in the Third World simply because so many more people lived there. The search for the gene causing Huntington's disease was immeasurably expedited by one enormous family in Venezuela; hemoglobin disorders were studied primarily among those who lived in the malaria belt (the Mediterranean basin, Southeast Asia, and parts of the Middle East) or whose ancestry could be traced there.

The call for Third World involvement was thus more than an empty gesture. Genetic disease was a serious problem in several regions, ranking among the most serious health concerns in the Mediterranean basin and parts of southeast Asia. Hemoglobin diseases were among the major killing diseases over large expanses of Africa and southern Europe. Diagnostic methods derived from genome research would be quite useful in the developing world, but only if they were inexpensive and reliable enough. Efforts to study diseases that primarily affected Third World populations would likely be neglected, and technologies to make tests cheap and simple might well languish without help from the technologically advanced countries.

HUGO was the great hope for finding a mechanism sufficiently durable to sustain vigorous international collaboration but flexible enough to avoid bureaucratic encrustation. It was a brainchild of the genome elite, founded on April 29, 1988, at the first annual Cold Spring Harbor meeting on genome mapping and sequencing. Victor McKusick circulated among the conferees, describing Sydney Brenner's notion of a new international genome organization. An impromptu session was scheduled at five in the afternoon. McKusick urged the thirty or forty individuals gathered in Grace Auditorium to form an organization modeled on the European Molecular Biology Organization (EMBO). Watson rose to reminisce about the early years of EMBO, which had been modeled on the European Center for Nuclear Research (CERN). Lee Hood endorsed the idea of a new organization to foster international cooperation and argued for an open membership structure and a strict focus on science. Sydney Brenner suggested the name HUGO, for Human Genome Organization (although he said he personally preferred THUG). Brenner urged that membership be by election, rather than open to all, and nominated McKusick as president of the new organization. McKusick was elected by those present.

McKusick followed up on May 3 with a memo summarizing the discussion, which he sent to a core group.[118] Those on the list were all senior biologists and constituted a presumptive founding council.[119] Bodmer and Matsubara soon pledged financial support, and the group planned a September meeting to begin the next steps.[120] The Howard Hughes Medical Institute funded HUGO's initial meeting to organize more formally in Montreux, Switzerland, on September 6–7, 1988.[121] The council had since expanded to forty-two members from seventeen countries. The Montreux group decided to focus on databases, physical mapping and sequencing, nonhuman species, ethical issues, and human disease mapping. The council drafted a brief organizational plan and elected McKusick president. Vice presidents were elected from Europe (Bodmer and Dausset) and Japan (Matsubara). The Montreux meeting was occupied in part with deciding between open and elective membership options. Those advocating elective membership won the day, although HUGO progressively diminished restrictions and eased the process of election between

1988 and 1990. HUGO's next efforts aimed to secure a financial base. Walter Gilbert was elected treasurer, and his first job was to find operating funds.[122]

HUGO weathered 1989 with great difficulty. Cash was scarce, and none of the organization's goals could be accomplished without it. In December 1989 there was only $25,000 in the bank. At a politically delicate meeting in Bethesda, Bodmer was elected president.[123] McKusick was named founding president, and the vice-presidential posts were designated by region. Matsubara stayed as vice president for Japan; Charles Cantor became vice president for the United States and Mirzabekov for Eastern Europe. Bronwen Loder performed most staff work in London, and ICRF footed the bill. Diane Hinton staffed the Americas office, on loan from HHMI. Loder and Hinton prepared a series of funding proposals to seek private funding so that HUGO could begin to operate.

The funding picture brightened in 1990, when the Wellcome Trust in the UK and HHMI in the United States both announced substantial multiyear grants to HUGO. Michael Morgan, from the Wellcome Trust, announced the award for 1990 "in the order of £200,000" ($350,000)[124] and said there would be further support over the next two years. HHMI announced a $1 million, four-year award to HUGO on May 3.[125] A week later, Cantor published a letter in *Nature* that described HUGO plans to coordinate physical mapping efforts chromosome by chromosome.[126] He proposed building on the existing Human Gene Mapping Workshops, which had committees for each chromosome and met at one large conference every other year.

HUGO hoped to go beyond biennial meetings to more frequent meetings focused on putting together maps of regions or chromosomes.[126] In July 1990, Wyngaarden was appointed executive director of HUGO, becoming the first permanent staff member. In August, the HUGO council agreed to Cantor's proposal to focus on chromosome-specific workshops. The HUGO Americas office would apply for funding from government agencies and private sources to hold the meetings, standardize the reporting format, and ensure speedy publication of individual workshop reports. HUGO would also search for a single facility that could be consistently used, enabling computer links to databases and possibly accumulation of a library and other resources.[127] As 1990 drew to a close, HUGO struggled to consolidate a financial base, to hire a staff in three offices (Bethesda, London, and Osaka), to track international developments, and to broker agreements on sharing data and materials.

As the genome project officially began in late 1990, it was clearer that HUGO needed to succeed than that it would actually do so. It proved difficult for an international organization to attract government funds. Most governments limited grants to domestic organizations, requiring HUGO to incorporate in each country or to seek a formal intergovernmental agreement. This was a slow and costly process. Many private funders also emphasized domestic interests. Another problem with private funding was its predominance in the United States, with one nation home to most foundations able to contemplate

grants of a size commensurate with HUGO's task (the Wellcome Trust in the UK and the French muscular dystrophy funds were notable exceptions). It was also extremely difficult to devise a staffing pattern that would retain substantial autonomy in each regional office (and hence attract good staff) but also enable coordination among offices on three continents. Most international precedents for international scientific projects were supported from the start by multilateral agreements or existing international organizations such as the UN or international scientific unions. These usually built from national government science agencies, coordinating science administration rather than scientists themselves.

HUGO attempted to reverse this strategy by starting from a private funding base and then cultivating government funding by applying for specific projects. The structure of HUGO was yet another new precedent that the Human Genome Project hoped to set. HUGO aspired to coordinate various national governments' programs through an organization established and directed by scientists. HUGO was based on the premise that the balance of power had shifted, so that scientists could exercise power over an international research program by creating their own organization. In a generous assessment of HUGO's accomplishments, John Maddox noted that "despite its modest successes so far, HUGO will find it has to keep running hard if it is successfully to play the ambitious role it has set for itself. The long-term objective is to command the respect of the world's genome sequencers individually."[128] HUGO had a long way to go, but then so did the genome project.

By 1993, the genome project was a well-established international effort. Nine countries and the EC each had one or more human genome programs. HUGO was five years old. At least six countries were actively considering whether to start genome programs (the Netherlands, Australia, Chile, Sweden, Korea, and New Zealand).[20;67]

In a 1989 column, political columnist George Will urged readers to "pay at least as much attention to science news as to political news. Political choices are made in contexts that politicians cannot choose, and the contexts are increasingly shaped by science."[129] Governments might not succeed in capturing the benefits of genome research for their domestic economies, but they could certainly try.

Management of the genome project was only partially within the reach of national governments, and yet government funding was, in most countries, its principal sustenance. The conflict between international scientific aspirations, to use the human genome as a vehicle for international cooperation, flew in the face of intense nationalist fervor premised on economic competition. The rhetoric of economic nationalism pervaded arguments across the Atlantic, but took a backseat to stronger and more established scientific norms of collaboration for the most part. Japan was a special case that brought trade tensions into sharp profile.

The genome project developed in a period when Western Europe sought unity and the former barriers to Eastern Europe were being dismantled. The early European genome efforts took origin almost simultaneously with the U.S. initiative. The Italian program, for example, can be traced to Renato Dulbecco's 1985 Columbus Day speech in Washington. The British and Russian programs developed in parallel with the NIH effort, formulated partially in response to DOE plans. The European Community program began soon after the first genome debates took place in the United States. The early European efforts thus trace their roots to the same sources as the U.S. effort.

A second wave of genome efforts was formulated in part to respond to the U.S. effort. In the context of a drive toward European economic and political unification, the rhetoric of keeping up with American programs crept into justifications for the genome program. This provided political justifications—preservation of national prestige and maintenance of a position in a field related to biotechnology—in addition to the original scientific rationale. Commitment to a genome research program became not only and end in itself, but a necessary investment to thwart American domination of an important frontier. The Canadian program shared this political justification with many of its European counterparts.

In the USSR, and then Russia, the genome project was relatively spared (although still seriously affected) by the turmoil that halted much science. This was because the originators of the program were associated with the reform movement from the start, the economic rationale behind the genome project was used from the beginning, molecular biology was widely regarded as a central filed for any future biotechnology, and the genome project carried a substantial fraction of all molecular biology. Molecular biology in the USSR had not attained the size and scope of its Western counterparts, in part because it had never fully recovered from the ravages of Lysenko. Only one full generation had passed. As the USSR dissolved, the Russian components of the Academy of Sciences attempted to sustain a genome program.

The importance of private initiatives proved an important feature of developments in Europe. The privately organized CEPH consortium greatly facilitated genetic linkage mapping. CEPH became even more powerful when it forged an alliance with the private muscular dystrophy association AFM. The resulting Généthon became Europe's most notable innovation in genome research, contributing to both genetic linkage and physical mapping. Its high-tech approach and heavy emphasis on automation created a prototype for similar centers set up later in the United States. In the UK, the private Imperial Cancer Research Fund became an equal partner with the government Medical Research Council. It also quickly adopted approaches intended to foster automation. The Wellcome Trust was an early supporter of the Human Genome Organization and came in to rescue an underfunded transatlantic collaboration. In 1992 and 1993, it stepped up its commitment to genome research, soon dwarfing the government contribution, and bringing the UK effort to

rough equivalence (per capita or relative to the size of the economy) with that of the United States, the only country that could claim such parity. The private support for genome research in the UK built upon a long-standing tradition of excellence in genetics and molecular biology greatly in excess of the nation's economy or even its biology budget.

These early contributions from nonprofit organizations in Europe paralleled the early involvement of the Howard Hughes Medical Institute in the United States, but their impact was relatively greater. This was, in part, because their relative financial contribution was greater. The government contributions to genome research in Europe were, by and large, imposed on relatively inflexible research bureaucracies, and the infusions of new funding were small by comparison to those in the United States, even after adjusting for the relative size of the national economies. The private funding sources were more flexible and their financial contributions relatively greater.

The hope for a European science may have driven some interest in genome research, but the structures to unify science were relatively weak. Most planning took place within the structure of individual government science and technology ministries. The European Community programs were notable exceptions. The EC successfully coordinated a highly complex collaboration that sequenced yeast chromosome 3, a major accomplishment, and previous EC biotechnology instrumentation programs figured in the creation of Généthon. The human genome component of the EC program was slow to start, however, because of concerns about its social implications, and the EC's genome research budget was no larger than the national programs. The EC efforts were thus important, but hardly sufficient to coordinate European programs to the same degree as NIH-DOE joint planning.

The rhetoric of European unity failed to translate into a carefully orchestrated genome research program, but it did succeed in garnering funds from various national governments. It also extracted commitments from the EC and various organizations supporting biological research throughout Europe, such as the European Molecular Biology Organization and the European Molecular Biology Laboratory. The desire for a more coherent program also led to cooperation among European governments. The European Science Foundation and Academia Europaea both commissioned reports on how to proceed, but even without those reports, the number of joint meetings and the degree of collaboration were unusual. The genome project thus served as an example of progress toward unification of science, but also an illustration of how far there was still to go.

15

Japan: A Special Case

In January 1872, thirteen-year-old Chokichi Kikkawa disembarked from the magnificent steamship *America* onto American soil. The young man looked for the first time at San Francisco Harbor, at one of the most beautiful cities on the continent that would be his home for the next eleven years. Kikkawa thus began his education in the ways of the West. He was one among one hundred Japanese in the Iwakura entourage, among the first delegations to venture out from Japan four years after the February 1868 enthronement of Emperor Meiji.[1] It was a revolutionary period, and the Iwakura entourage was among the first of many human connections to America established after Commodore Matthew Perry forced open Japan's doors.

Takayoshi Kido, a former samurai, was also on board the *America*. Kido was one of the three principal leaders who restored power to the emperor in the tumultuous 1860s.[2] Kido was sent to the United States to renegotiate the terms of treaties signed in 1854 and 1858, documents that granted the United States access to Japan. The *America*'s voyage began with great fanfare at 1:00 P.M. on December 23, 1871, when it left from Yokohama to the echoes of a nineteen-gun salute.[3] Kido did not succeed in renegotiating the treaties, but the trip produced a wealth of knowledge about the outside world for a Japan craving just such information.

Commodore Perry, a hero of the Mexican War, ended Japan's two centuries of nearly complete insulation from foreign influence that began with a 1638 decree from the Tokugawa shogunate. When the American "black ships" sailed into Naha Harbor in May 1853, the threat of foreign military power disrupted Japan's internal order. Superior arms and foreign technology shattered the crusty feudal regime. Perry's fleet included steamships, which were quickly replacing the famed American clippers, and he brought novel technologies—pistols and rifles, a telegraph, and even a locomotive engine complete with one car and several hundred yards of track.[4] Perry and his new technology thus cracked the wall that had separated Japan from the rest of the world. He ended the Tokugawa era—two and a half centuries of rule under the shoguns.

The technology of sea travel overcame the geographic barriers that kept Japan separate; advanced foreign military technology made Japan vulnerable.

The importance of technology left a strong imprint on the newly exposed Japan. After a decade and a half of chaos and intrigue, Emperor Meiji gained power in 1868. Japan's leaders recognized the degree to which the nation had fallen technologically behind the West and aggressively promoted policies to catch up. The emperor asserted that "knowledge and learning shall be sought after throughout the whole world, in order that the status of the Empire of Japan may be raised higher and higher."[5] Thus began a trend that persisted throughout the twentieth century. Those who went abroad were sources of knowledge useful in modernizing Japan. Kido and Kikkawa were among the pioneers, human bridges from Japan to the West.

Takayoshi Kido returned to Japan in 1873, maintaining his role as imperial councillor and helping to dismantle feudalism in Japan. He became a leader in reform movements and helped establish a constitution modeled on Germany's, doing much of the writing himself. Kido was regarded as "the most liberal and humane member of the government, even as his power waned."[2] Among the "Meiji triumvirate" who engineered the emperor's resurgence, Kido alone died of natural causes. The second committed *seppuku* (ritual suicide by stabbing the viscera) later in 1877, and the third was assassinated by disgruntled samurai the following year.[2] Kido spent his last years criticizing government policies that impoverished his former samurai brethren and the peasantry. The teenage Chokichi Kikkawa had a less treacherous if more meandering road home from America.

Young Kikkawa traveled by train from San Francisco to Boston, where he stayed from March to August 1872 with the Rev. Charles Nathaniel Folsome, who ran his household according to rigid puritanical precepts. Kikkawa learned to revere strict personal habits and dedication to objective truth. He then spent a year at the Rice Grammar School and another four years at Chauncy Hall School. He graduated *summa cum laude,* with an award for English composition. In June 1879, Kikkawa passed his entrance examination for Harvard, and matriculated there in October, living in 23 Matthews Hall. He was among Harvard's first Japanese graduates, perhaps its first. He graduated in 1883 and set sail for Europe.[1]

Kikkawa returned to Japan in December 1883, twelve years after the voyage on the *America* began. He was persuaded to join the Foreign Office by the foreign minister, serving in Tokyo from 1883 to 1886 and then in Germany for four years. He returned to Japan in 1890, joined the House of Peers, and was married in 1892.

Kido's and Kikkawa's families reunited to form another human bridge to the United States on June 28, 1929, with the birth of Akiyoshi Wada—great-grandson to Kido and grandson to Kikkawa, from a different branch of the family tree. His father, Koroku Wada, was president of the Tokyo Institute of Technology, dedicated to advancing Japanese technologies in space and aeronautics. Technology ran in the family. Akiyoshi Wada studied at the point of

intersection between physics and chemistry and ultimately worked in biophysics. His contact with the United States was solidified when he spent 1954 to 1956 working on protein structure with Paul Doty of Harvard, where he learned "the basic spirit of science, which is to serve mankind."[6]

Wada became a critical figure in DNA sequencing before the genome project was conceived as a special program. In 1981, Wada was appointed chairman of a project named "Extraction, Analysis, and Synthesis of DNA." This was supported by a special fund from the Science and Technology Council of Japan, funded through the Science and Technology Agency (STA). The project had two aims: to reduce the tedium of biological research and to engage the interest of companies from outside biology, including firms whose technology base was robotics, electronics, computers, and materials science.[7] Wada's strategy was to automate existing protocols used in molecular biology rather than to invent entirely new approaches.

The project focused on DNA sequencing because it was clear it would become increasingly important. Japan was greatly interested in robotics and automation, and it was thought relatively straightforward to automate laboratory processes involved in DNA sequencing.[7-9] Wada enticed Seiko, Fuji Photo, Toyo Soda, Hitachi, and Mitsui Knowledge Industries to join the project team.[7] This first phase, 1981–1983, was funded at ¥910 million ($3.7 million at the then-current 240¥ / $). It produced a microchemical robot made by Seiko and a standardized electrophoresis gel system made by Fuji Photo. In 1984, the project was funded again under another branch of STA, now titled "Generic Basic Technologies to Support Cancer Research" and funded at ¥450 million (or $2.05 million at the then prevailing rate of 220¥ / $). Seiko developed a DNA purification system and another microchemical robot, Fuji began to mass-produce its gel, and Hitachi developed a prototype DNA sequencing machine.[10]

The base of operations was moved as a "Research Project on Gene Composition" to the RIKEN Institute in Tsukuba Science City (officially, the Institute of Physical and Chemical Research, or RIKagaku KENkyusho). The RIKEN Institute was established in 1917, during the Meiji era, with support from the imperial household, government, and private sources. Just before and during World War II, RIKEN was the home of Japan's efforts to develop an atomic bomb,[11] providing yet another historical link between genome research and bomb projects. The Tokyo laboratories were largely destroyed in the war, and the institute was reestablished in 1958.[12]

In 1985, Wada's DNA sequencing project was swept into the debate about a human genome project. The connection was Charles DeLisi, who explained:

> In 1985 when I was director of the Department of Energy's Health and Environmental Research programs, I was impressed by the need for a more efficient and cost-effective approach to DNA sequencing. When we started developing the Human Genome Project . . . it was picked up by the American press as a new and bold initiative. In fact, it was not at all new in Japan. I received a note from Minoru Kanehisa [who had

worked at the GenBank database at Los Alamos National Laboratory before moving to Kyoto University] indicating that a similar project had been initiated there five years earlier. . . . My old colleague, Professor Wada, whom I had known through his distinguished contributions to a somewhat different area, turned out to be the person to speak to. . . . It became obvious that he had already done what we were just beginning to think about. . . . Just this one initiative alone would have been sufficient to rank Professor Wada as a major figure in world science, and a hero of Japanese science and technology.[13]

Akiyoshi Wada, who headed a Japanese project to automate the biochemical processes involved in determining DNA sequences in the early 1980s, later led attempts to organize an international genome project. Wada's efforts were particularly influential in stimulating the U.S. program. *Courtesy Akiyoshi Wada*

In late 1986, Wada came to the United States, seeking support for an international DNA sequencing effort, hoping to consolidate an international base of support for his project. He met with those involved in the nascent human genome debate in Washington, at the National Institutes of Health, the Department of Energy, and the Office of Technology Assessment. He also visited several research centers, including Los Alamos National Laboratory, and returned to Los Alamos to speak at a workshop on robotics in January 1987. Wada's vision was a series of international centers dedicated to rapid, inexpensive DNA sequencing. He thought that Japan would be an early leader in automated DNA sequencing, and it would be logical for Japan's efforts to concentrate on that strong suit. He intended large-scale DNA sequencing to be a unifying force, bringing the United States and Japan closer together through collaboration. The politics of the day would not have it so.

Wada's interest in visiting the United States was not only to form new collaborations with American scientists, but also to generate political support for his project in order to bring foreign pressure on Ministry of Finance bureaucrats back in Japan. Wada was following an established strategy, *gaiatsu,* using foreign presence to pry funds loose from the Japanese government, notoriously stingy in its support for basic biology. Press reports from abroad

could be used as ammunition in the battle to capture funding, essentially embarrassing the Ministry of Finance into loosening the purse strings.

Wada obtained continued funding for the RIKEN project, although not at the levels he desired. He had hoped for a major commitment to a large sequencing center; what he got was a continuation of the RIKEN research effort. Indeed, his colleagues in Japan faulted him for raising hopes too high and for exacerbating tensions between the United States and Japan by scaring Americans with a high-profile project.[14;15] Critics also pointed out that industrial partners were abandoning the project, that Seiko was not marketing its machines, and that Hitachi was selling its sequencer only in Japan. Hitachi left the project, and Fuji was about to do so. The Fuji ready-made gels for DNA sequencing were test-marketed, but then quietly withdrawn. Wada became preoccupied with other projects, as he became dean of the faculty of sciences at the University of Tokyo and worked toward reforming science in Japan.

In 1988, the reins of the automated sequencing project were turned over to Koji Ikawa and Eichi Soeda at RIKEN. They reassessed the technical objectives and concluded that initial cost and speed estimates were too optimistic.[16] The goals were scaled back to a sequencing capacity of 100,000 DNA base pairs per day, down from Wada's million. By 1989, the automated DNA sequencing project had been under way for eight years, yielding a set of machines capable of sequencing roughly 10,000 bases per day.[16] A new series of projects, to automate cloning and other processes in molecular biology, was commenced under Isao Endo of RIKEN. Endo's project bore fruit in June 1991, when he reported it had attained a potential raw output of 108,000 base pairs per day.[17;18] The project involved ¥ 600 million ($4.5 million) from STA over the decade, and an unknown total of in-kind expenses from Hitachi, Seiko, Cosmic, Mitsui Knowledge Industries, Tosoh, and Fuji Film. The sequencing part of the system, humorously named Human Genome Analyzer or HUGA, was a fluorescence-based DNA sequenator made by Hitachi.

STA also began to fund selected projects in universities, including chromosome mapping on chromosomes 21 and 22 under Nobuyoshi Shimizu at Keio University. The annual STA genome budget was approximately ¥200 million ($1.3 million) in 1989 and 1990[16;19–25] and rose to ¥1.2 billion ($8.6 million) in 1991.[17] The 1991 STA program commenced a formally approved extension of the previous pilot projects, with specific component projects led by Eichi Soeda (RIKEN), Masaaki Hori (National Institute of Radiological Sciences), Isao Endo (RIKEN), Joh-E Ikeda (Tokai University), and Hiroto Okayama (Osaka University).[26]

The RIKEN DNA sequencing project was pulled into the vortex of American debates about genome research. It was not used to promote cooperation, however, but rather to goad the U.S. government into funding the American genome project. The Japanese sequencing project was held up to Congress as evidence that Japan had a five-year lead in a crucially important technology. This surfaced in the first, critical congressional hearing on the DOE project.[27]

Congressman David Obey noted in hearings associated with NIH's first genome budget that "given the competitiveness issue which we have in this country, and the trade issue . . . it sounds to me like this argument is about to be couched in terms of them versus us."[28] Indeed it was.

Senator Pete Domenici commented on the Japanese genome project in his opening statement for a field hearing on the genome project in Santa Fe, New Mexico, in August 1987: "It came to me very quickly during the debate on so-called trade and competitiveness that an issue such as the mapping and sequencing of the human genome . . . while terribly important in terms of our understanding diseases and being able to cure them, that it was becoming a very, very significant competitive situation, vis-à-vis at least the Japanese, but not limited to them."[29] Staff in Congress (not Domenici's) discussed adding riders to NIH appropriations forbidding purchase of Japanese instruments under federal grants, or restricting NIH funding for foreign postdoctoral and graduate students. These discussions did not bear fruit, but their existence clearly indicated the dominant congressional concerns.

Wada's bridge had become a wedge, driving the countries apart. In the United States, the Japanese effort was seen as a technological threat, and another instance of Japan neglecting basic science in order to promote work on development of something that could be exported and sold, in this case DNA sequencing machines. The Japanese genome project got stuck in the tarbaby of U.S.–Japan trade tensions.

American perceptions of the Japanese genome project as a biotechnological Trojan horse—a premeditated assault on one of the remaining bastions of U.S. preeminence—were grounded more in loose historical analogies with automobile manufacture and electronics than in direct observation of the policy process. The Japanese genome program as a scientific effort was largely the result of scientists aspiring to join the international ranks. Industrial partners were, at least in the opening phase, more reluctant participants than instigators. The genome program was more a dream of what Japanese science could become than a cornerstone in some grand economic plan.

Ken-ichi Matsubara tried to broaden Japan's genome effort by giving it a stronger academic grounding. Matsubara was the director of the Institute for Molecular and Cellular Biology at Osaka University. He got his bachelor's and Ph.D. degrees from the University of Tokyo, then did postdoctoral fellowships at Harvard and Stanford. Most of his work was at the interface between molecular biology and biochemistry, looking at the process of cancer formation in the liver and also at how hepatitis viruses infected liver cells. He became director of the Osaka institute in 1982.

Following press reports of emerging genome projects, Matsubara visited the United States with a small group in February 1988. He was an adviser to the STA project, but had hopes that the Ministry of Education, Science, and Culture (MESC, commonly known as Monbusho) could also be drawn in,

perhaps on a larger scale than STA. Monbusho funded the vast majority of academic science in Japan, principally at the nine major universities and forty or so smaller universities throughout the prefectures. Monbusho's university base contrasted with STA's emphasis on government-funded laboratories and institutes. Matsubara hoped Monbusho would make genome research a priority area, beginning in the 1989 budget.[23]

When Matsubara returned to Japan, he became chairman of a group advising Monbusho. Monbusho did indeed smile favorably upon genome research, giving it ¥300 million per year for 1989 and 1990 ($2 million per year at ¥150 / $). This commitment to a pilot project, quite significant by Japanese standards, did not seem as grand to those outside Japan. The issue came to a head in the fall of 1989.

The dark clouds gathered slowly. The potential for conflict loomed in the background of the first international conference on the Human Genome Project, held in Valencia, Spain (October 1988). As noted earlier, this lavish conference was organized by Santiago Grisolía, a Spanish biochemist greatly intrigued by the genome project. By the time of the Valencia meeting, the DOE project was beginning its third year and NIH its second. Italy, the UK, the USSR, and the European Communities had described their respective genome programs at a session presenting efforts from around the globe. Yoji Ikawa described the STA sequencing project and mentioned the Monbusho project, then in planning phase. The annual budget was comparable to Italy's, but far lower than those of the EC, USSR, and UK programs. There was some comment to this effect after the session, but in muted tones and only outside the formal session.

The next major meeting on international collaboration was held in Moscow, in June 1989. The meeting, cosponsored by UNESCO and the USSR Academy of Sciences, featured James Watson, Walter Gilbert, Victor McKusick, François Gros, Charles Cantor, and several other luminaries. Soviet academicians Andrei Mirzabekov and Alexander Bayev hosted the meeting, considering it an opportunity to showcase the Soviet genome project. By then, the STA project in Japan had secured another two-year funding commitment and the Monbusho project was getting underway. Matsubara had completed a pair of documents outlining the Monbusho strategy,[30] and a similarly favorable report had been completed for STA.[31] Matsubara could not attend the Moscow conference because a colleague died, leaving Ikawa as the lone Japanese representative.

Watson pulled Ikawa aside on the steps of the Hotel Ukrainia, one of Stalin's seven "wedding cake" skyscrapers in Moscow, to indicate his irritation. Watson asserted that Japan was now a great nation with vastly greater resources than any country except the United States, and Ikawa should go back to Japan and tell his government to put more funding into genome research, or there would be problems. Watson hinted that Japan was becoming isolated by its niggardly ways, and if need be, the United States would make access to

databases and research materials difficult. Absent a bigger commitment, Japan would be shut out of planning the international enterprise. Honest Jim Watson was apparently carrying on the mission of Commodore Perry.

Watson was in the process of deciding whether to visit Japan later in the year. Matsubara had invited him to visit Japan to meet fellow scientists and government officials, among other things to convince them of the importance of genome research. Watson was ambivalent because of his experience years earlier, when Itaru Watanabe attempted to establish an Asian molecular biology organization. Watson went to Tokyo to support that effort, but it came to naught, devolving into a nasty fight between Watanabe and government officials. Watson recalled a meeting when "they behaved like twelfth-century shoguns." Watson did not want to be similarly used again. He indicated that he would come only in response to a signal that the government was ready to deal.

In July, Watson wrote to Matsubara that he would not be coming to Japan. He went on to urge Japan to ante up by supporting the Human Genome Organization and to bolster basic science funding. Watson testified on October 19, 1989, before the Subcommittee on International Scientific Cooperation of the House of Representatives.[32] Japan inevitably came up. Soon Leslie Roberts, a reporter for *Science,* found out about the Watson letter to Matsubara by talking to American scientists embarrassed about it. Watson declared, "I'm all for peace, but if there is going to be war, I will fight it."[14] After this outburst, other scientists opened up and released copies of Watson's letter. Roberts quoted from Watson's letter and Matsubara's reply in a *Science* news feature, "Watson versus Japan."[14] This made the spate public, and it was echoed elsewhere.[15; 33–35] In the United States it was seen as another Watson temblor; in Japan the quake was larger and left more rubble. In *Asia Technology,* the story was about "The Human Gene War."[15]

John Kendrew spoke for many in the scientific community when he scribbled a note to Watson: "I hope this report is not true, because if it is, you should be ashamed of yourself! All the best for 1990."[36] Watson shot back a crisp reply:

> I am not ashamed of myself. The issue now is whether to make the human sequence data available to all before those labs which have generated megabase stretches have a first go at their interpretation. Your LMB [Laboratory of Molecular Biology, Medical Research Council] did not distribute broadly its viral sequences before they were published. . . . The UK seems resigned to becoming economically a Japanese colony, but there are many of us in the States who will fight like hell to prevent a similar situation. With the Cold War gone, at last we have a chance to ask where we are going. See you in Paris (?)[37]

Japanese scientists were particularly incensed at the paternalistic tone of Watson's letter to Matsubara. While allowing that he was correct to say the

Japanese government was giving insufficient funding for basic research, they deeply resented the public humiliation. Many ascribed Watson's remarks to racism or fashionable "Japan-bashing." This underestimated the degree to which Watson captured what irked Americans and Europeans about Japanese science policy. Watson had expressed admiration for Japan, and had urged that the United States imitate its macroeconomic policies at a Harvard University talk a year earlier.[38] If his words were Japan-bashing, they were not of the simple-minded xenophobic variety.

Several Japanese scientists saw a policy advantage for them as a result of the furor. Privately they hoped the publicity would put pressure on the Japanese government to increase research funding. Michio Oishi noted that Watson's strong focus on genome research and his insistence that Japan do its part made Japanese government bureaucrats take notice.[39] This was again a classic instance of *gaiatsu,* bringing foreign pressure to bear on the Japanese government when domestic pressure was ineffectual. If the strategy was to create foreign pressure for government funds, then Watson was the ideal messenger; it certainly made the papers.

A year after his unpleasant encounter in Moscow, Ikawa explicitly acknowledged the impact of Watson's statements in a January 1991 summary of Japanese genome efforts, saying that "Dr. J. D. Watson has criticized the inadequacy of Japanese participation." Ikawa closed his article by noting that Watson had visited his laboratory twelve years before and expressing his hope that "this review will aid him and others outside Japan to understand this country's slow but steady movement forward in this important field."[40] The article was clearly aimed at Watson.

The U.S.–Japan dispute did not become news until late 1989, but it was anticipated in Washington for some time. Aki Yoshikawa, who wrote a commissioned paper on Japan for the Office of Technology Assessment in 1987, concluded the paper with the observation that "efforts to cooperate by well-meaning scientists from the two countries . . . may end up in conflict."[41] The conflict grew out of competing goals—free international exchange of scientific data, on one hand, and economic nationalism regarding biotechnology, on the other. Factions espousing free scientific data flow and others emphasizing economic competition contended for the upper hand in both countries. Yoshikawa noted:

> Japanese scientists do not have credibility problems—the quality of Japanese science is well recognized elsewhere in the world. Japanese scientists are eager to conduct research with American colleagues. However, it is the process of Japanese policy formulation—the role of bureaucrats and the close ties between government and business in Japan—that foreign observers have sometimes questioned. . . . Although friendships within the scientific community may be sufficient to bring an informal "small" project to fruition, a "large" science project that requires commitments from more than two governments as well as scientists is a more complicated matter.[41]

A mechanism to match benefits to contributions, with each country paying a proportionate share, was difficult to envision. Governments were pursuing policies to bolster national commercial interests. Industrial competitiveness was the policy buzzword of the day, and it was much heard in Washington.

The genome project, because of its timing and its high-tech, whiz-bang aura, was coupled directly to biotechnology, and thence to industrial competitiveness. In covering U.S.–Japan competition in technology, *Time* gave considerable weight to the genome project, indeed more than its due: "The centerpiece in the U.S. response is the government's mammoth effort, known as the genome project."[42] *Roll Call,* a newspaper widely read on Capitol Hill, ran a special feature on competitiveness in July 1989, centered on the Japanese threat to American dominance in technology. Senator Domenici had the lead article, and cited the genome project as a case where the United States had to remain in front.[43]

It was clear that the United States was preeminent in biotechnology. Analysts differed markedly, however, in assessing the future. Some, including the U.S. Department of Commerce, believed that the major contenders would arise in Europe rather than Japan.[44] Others, including the Office of Technology Assessment, believed Japan would figure more prominently.[45] The debate centered on two factors with opposing trends: the importance of deliberate government interventions to foster technology and the importance of a solid scientific base.[46] In other industries, Japan had successfully promoted economic expansion through targeting specific areas of technology; biotechnology was now targeted for special treatment. The United States was clearly ahead in science, but it was a matter of debate whether science could be confined within national borders.

Some believed that Japanese government policies would have little impact on biotechnology,[47] while others thought Japan's targeting of biotechnology would confer a critical edge to Japanese industry.[48–51] A 1991 OTA report noted that "there are two prerequisites for a nation to fully compete in biotechnology: (1) a strong research base and (2) the industrial capacity to convert the basic research into products."[46] The United States was clearly preeminent in research, but the health of its industrial capacity and policies to foster the translation from science to product were less certain. OTA noted that the U.S. science base remained the world's most robust. Japan had strong industrial policy direction and a strong track record in applying new technologies in other industries, but was relatively weak in the industrial sectors most relevant to biotechnology—pharmaceuticals, agriculture, and environmental remediation.[46] Europe had a strong research base, although it was far more fragmented into national programs, and had strength in the relevant industrial sectors, but the climate of public opinion was turning sour for biotechnology regulation.

One salient feature of U.S. biotechnology was a group of more than four hundred dedicated biotechnology companies. These were relatively small and

new firms, most of which sprang up between 1980 and 1984. Other countries had a few such firms, but there were far more in the United States. These companies had grown in parallel with the power of genetics and the recognition that the science would find commercial application. A web of intertwined relationships developed between U.S. university scientists, small and large biotechnology companies, and Japanese firms, in all combinations and in a complex mix of arrangements.[52;53] Analysis of how these arrangements would play out was confused by the ambiguous status of multinational corporations, whose interests resisted simple classification according to where the headquarters were located.[54–56] The main conclusion, however, had to be that these firms were the engines of innovation in U.S. biotechnology, but their precarious financial position invited investment by foreign firms (and larger U.S. firms). Small biotechnology companies were a national asset, but were a channel of technology transfer abroad, and were vulnerable to purchase or domination by foreign forms.

A 1992 report from the National Research Council studied the flow of ideas between the United States and Japan, principally via agreements between large Japanese firms and small U.S. biotechnology companies. It focused on the main trend—ties between small U.S. dedicated biotechnology companies and large Japanese pharmaceutical, chemical, and agricultural companies. The report concluded:

> Despite the strengths of the U.S. biotechnology industry today, the NRC working group is not sanguine about the future and the ability of the U.S. biotechnology industry to compete in the twenty-first century. Significant potential problems were identified that cannot be adequately addressed on an ad hoc basis because active collaboration of government, industry and universities will be needed.[57]

Given the high stakes of the outcome and the vast cultural disparities, the debate about international competition and biotechnology was vigorous and emotional. The genome project was but a small vessel sailing through the rough seas of international trade tensions.

The Watson-Matsubara correspondence embodied the global conflict in microcosm. Matsubara bristled at the fact that the U.S. government created a program and then apparently expected the rest of the world to play by its rules. Watson resented the fact that the world's second most wealthy nation was apparently content to freeload off other countries' research, focusing only on those aspects that promised economic payoff in the form of exportable goods. The genome project caught the United States reeling economically from a decade of mismanagement of its banking and financial sectors, overwhelmed by debts, excessive defense spending, and the inexorable expansion of federal entitlement programs. Japan, in contrast, exuded confidence while the genome project was first formed. The 1980s were stacked atop four decades of consistent economic growth that transformed Japan into the second-largest eco-

nomic power, one with a growth rate well in excess of that of number one, the United States.

Japan was completing a decade of remarkable economic expansion, although the rate of expansion slowed in 1989 and 1990 and declined even more sharply through 1991 and 1992. Unbridled optimism slowly gave way to a more temperate view. Japan nonetheless boasted seven of the world's ten largest banks and assets valued greater than those of any other nation, in large part because of the extremely high cost of land and housing on the densely populated islands. The future of the Japanese economy was less certain than it had seemed in the era of unrestrained self-confidence, as competition within the Pacific basin intensified, Japanese stocks plunged by more than a third, and real estate values—the main asset of many economic heavyweights—became unstable, having become so outrageously high that government action to control spiraling land inflation seemed inevitable.

The United States, for its part, had considerable doubts about its economic future. In 1991, the nation reasserted its military might in the Persian Gulf, but the underlying economic strength was more questionable. In 1991, U.S. biotechnology firms raised a record $17.7 billion in public offerings, and biotechnology stocks rose,[46] but a protracted recession cast a pall over national policy and intensified doubts about the underlying strength of the U.S. economy. The debate about long-term competitiveness remained a subject of much speculation, particularly relative to Japan. The U.S.–Japan relationship had to adapt to circumstances starkly different from those prevailing during the 1950s and 1960s, when most of the framework for interactions had been constructed.

As Japan in the 1970s and 1980s demonstrated its technological prowess, becoming the world leader in consumer electronics, automobile manufacturing, and other areas, its technological preeminence was oddly wedded to neglect of basic science.[58] Research was much more heavily supported by government in the United States than in Japan. In the United States, government supplied almost half of all research and development dollars, compared to one in five for Japan.[59] Specifically in biotechnology, the U.S. federal government expended an estimated $3.5 billion in 1990, and industry another $2 billion.[60;61] The U.S. federal contribution was even more dominant in biotechnology than in other parts of research and development, while in Japan, the government funded at most a quarter.[46;57] The obvious inference was that U.S. funding went predominantly to basic research whose results were published and shared, while private funding in Japan was more focused on specific corporate interests.

The enigma of Japan was not new. In 1877, a British commentator noted the logical and dedicated education given to engineers in Japan, as an early reform of the Meiji era.[62] In 1904, Henry Dyer wrote to *Nature* that "all the latest applications of mechanical, electrical, and chemical science have been

freely and intelligently employed. . . . The inventions and improvements which have been made by Japanese officers, engineers, and scientific men disprove the charge, which is very often made, that the Japanese have no originality. Even in the matter of pure science, Japanese investigators have shown that they are able to take their places among those who have extended the borders of knowledge."[5] He could have written the same text nine decades later. Japanese dedication to technology long predated World War II.

The decentralized and feudal organization of the science bureaucracies harked back to the Tokugawa era. A May 1990 Department of State memo on genome efforts in Japan observed: "Government of Japan Ministries continue to conduct human genome research efforts independently of any government-wide coordination. . . . Japanese participation [will emphasize] commercial applications rather than . . . basic science research."[63] In 1990, aggregate funding for the genome effort in Japan was estimated at between $5 and 7 million, depending on how costs were counted—more than tenfold lower than the U.S. government contribution through NIH and DOE in absolute terms, or sixfold lower relative to GNP.[16;34;64–68]

There were indications, however, that Japan might be changing. From 1985 to 1987, Japan moved from fourth among nations to second, behind the United States, in number of scientific papers published.[69] Japanese science attained world standards in more and more areas. Japanese papers were numbers two and three in the list of top ten papers cited in biology in the second half of 1989.[70] Japanese groups had international stature in some areas of molecular neuroscience, biophysics, and other fields. The United States consistently contributed 35 to 45 percent of the articles on human gene mapping and sequencing in the decade 1977–1986, more than twice the share of any other nation, and roughly comparable to the total for all Western European nations combined. Japan contributed only 2 percent in 1977, but showed consistent growth to 5 percent by 1986[71] and to 6.1 percent by 1990.[72]

Japanese science was spotty, but the spots were growing in number and size, and the bright spots were luminous indeed. The system of funding was antiquated and inflexible, but complaints were being aired publicly,[68;73;74] offering some hope for remedy. In part because genome project planning was new, it incorporated reforms. The Monbusho proposal for 1991–1996 included funding for postdoctoral students, otherwise lacking in Japanese biology, and also followed the worldwide trend to include a program in "ethics."[75] If this trend continued, support for basic science might grow as the linkage between science and technology became apparent, the types of technologies ripe for commercialization increasingly blended with basic research in biology, and as Japan became more conspicuous as a world power responsible for shouldering a burden for providing the world with public knowledge. But tomorrow was not here, and the prevailing ethos—fear of Japanese technological domination—colored international genome politics.

Watson faced intense pressures in Congress not to "give away the family jewels," in the form of public data generated at U.S. taxpayer expense. On a personal level, Watson regretted having written the Matsubara letter as he continued to face hostile questions about threats to withhold scientific data.[76] At a June 1991 international conference on ethical aspects of genome research, Watson and Matsubara shared the stage.[77] Not a word was spoken about restricting access to databases or stock centers. The emphasis was much more on building an international support system to fund worldwide databases and other shared resources. The storm was finally spent between the two principals, although it continued between their governments.

In Japan, biologists knew of their sorry state in comparison with their industrial counterparts and wished for a bigger slice of the national economic pie. Policy was dominated by bureaucrats and industrial interests only slowly learning the connections between science and technology, quite distant from the science base. The difficulty of forging a coherent plan was made clear by the proliferation of bureaus mounting genome projects. For scientists in Japan, the future might be bright, but it seemed a long way off.

The STA and Monbusho projects sought substantial budget increases to begin in 1991.[40;78] The Monbusho plans crafted by Matsubara and the scientific advisory committee were trimmed by Monbusho officials in the fall of 1990. The Ministry of Finance, responding to the paucity of government funds, cut even more deeply. *Nature* noted the dousing of scientist's ambitions under the headline "Japan's Project Stalls."[79] Monbusho and the Ministry of Health and Welfare eventually got 1991 budgets of ¥400 million ($2.96 million) each.[17;80] As budget negotiations began for 1992, the Monbusho program appeared likely to plateau far below the aspirations of its university proponents, while the STA genome budget surged ahead with a 50 percent increase.[81]

In addition to the Monbusho and STA programs, the Ministry of Health and Welfare mounted a genome research program that concentrated on disease-associated human genes and new technologies to find them.[82]

The commitment to the study of ethical, social, and legal issues paralleled the U.S. and EC efforts, but the degree of commitment was dramatically less. The Monbusho and Ministry of Health and Welfare programs each had such components, but they constituted a much smaller fraction of a smaller budget than their European, American, and Canadian counterparts. The Monbusho "ethics" program was directed by Norio Fujiki of Fukui Medical School, but its annual budget was $30,000,[83] a paltry sum. Tadami Chizuka, a professor of European history at Tokyo University, had a similar budget of ¥5 million ($37,000) from the Ministry of Health and Welfare, most of which went to translate genome policy documents from abroad.[83] Japan hosted a major international bioethics conference on genetics, which generated the Declaration of Inuyama.[84] Bioethics in Japan, however, was clearly not at the same

stage of evolution as in North America or Europe, and was unlikely to grow in the absence of a commitment by academic centers and government funders.

The Ministry of Agriculture, Forestry, and Fisheries announced a ¥621 million ($4.1 million) 1991 budget to map and sequence the rice genome. This was later scaled back to ¥372 million ($2.7 million), and raised questions about the commitment of Japanese industry to the project and the degree to which information would be shared or closely held by participating companies.[85] By 1992, however, the rice genome project had a dramatic resurgence, fueled by the Japanese practice of funneling a quarter of the proceeds from horse-race betting into science and technology projects. When it came to horse-race funds, MITI and the Agriculture Ministry had the inside track on the universities and the Science and Technology Agency.[86] In a reversal of the human genome pattern, it was the American scientists who came from their government empty-handed, the U.S. Department of Agriculture fearing a long line of researchers seeking genome research funds for their particular crop plant.

Even as the science agencies in Japan cried poverty and pointed to the future promise in their domain, and Ministry of Finance bureaucrats trimmed the wings of their nation's best scientists, the Chiba prefectural government and private corporations announced plans to build the Kazusa DNA Research Institute, on the opposite side of Tokyo Bay from Japan's capital.[87] The advisers to this project overlapped extensively with those advising the four government agencies: Monbusho, the Science and Technology Agency (STA), the Ministry of Health and Welfare (Kosei-cho), and the Ministry of International Trade and Industry (MITI). One part of the Chiba project, led by Mitsuru Takanami of Kyoto University and slated to start in 1993, was to serve as a nonprofit DNA sequencing center for Japanese laboratories. Another part was to focus on technology development, research, sequence analysis, and structural biology.

The DNA research institute was to be a centerpiece in the Kazusa Academia Park, a magnet for private industrial research institutes. Itaru Watanabe and recent Nobelist Susumu Tonegawa were influential in convincing Chiba prefectural officials to support the institute, securing ¥5 billion ($37 million), most of which was from the prefecture but some of which was in the form of contributions from Nippon Steel, Tokyo Electric Power Company, Tokyo Gas, Hitachi, Mitsui Toatsu Chemicals, and local banks. By 1991, the pool of funds stood at stood at ¥9 billion ($67 million). The institute was said by prefectural officials to be "unrelated" to genome plans by various agencies in Japan; to outsiders it seemed that the Kazusa institute was as unrelated to the Human Genome Project as a son is to his father. Its power base was indeed different, because the people championing it were different, and so to its Japanese sponsors it may have seemed unrelated. To the outside world, the

functions it would perform were clearly related to genome research, however, and so it seemed integral to some larger plan. But there was no such master plan.

This numbing litany of budgets amounted to roughly ¥2 billion ($15 million) for the nonagricultural parts of government-supported genome research,[17] compared to $160 million in the United States. This was a significant increase from 1990, but still small by comparison. The figures were not strictly comparable, however, as the Japanese budgets did not include salaries, which would have boosted their funding to the equivalent of $21 million. Despite the Ministry of Finance cuts, the higher funding levels in 1991 brought Japan to rough and transient parity with the United Kingdom, surpassing genome funding in all other countries except the United States, after adjusting for GNP.[19;25;88-92] (In 1993, the U.K. again surged ahead through an infusion from the Wellcome Trust.)

Meanwhile, the powerful Ministry of International Trade and Industry (MITI) was hatching plans of its own. MITI hoped to use excitement about the genome project to galvanize the interests of corporations not hitherto associated with biology. An official within MITI first floated the idea of a genome program in 1987. Sumitomo Electric picked up the signal and responded with enthusiasm.[33] Michio Oishi of Tokyo University was designated the academic contact for planning the MITI foray into genome research, which was intended to welcome companies from electronics, robotics, and other sectors. Project planning in academia was spearheaded by Oishi, while industrial support was organized by the Japan Biotechnology Association, a private organization interposed within the triangle defined by MITI, academia, and industry.

The Japan Biotechnology Association linked the three vertices of this triangle, incubating ideas and staffing the activities necessary to generate consensus behind new initiatives. The idea of the MITI project was to improve research instrumentation, to cultivate interest in basic biology among powerful industrial interests new to the field, and to encourage a long-term commitment by a consortium of companies using a mix of roughly equal portions of government and private funding.[89;90] MITI conferred its blessing on the Kazusa DNA research institute, lending it stature and credibility, although the ministry committed no funds to its operation.[87] It seemed likely that in the ensuing years, when that institute opened its doors, MITI might have a substantial effort of its own underway.

The genome project thus spawned programs in several ministries, whose planning processes and basic constituencies were for the most part separate. Wataru Mori, a member of the Science and Technology Council that advised the prime minister, attempted to bring some coordination to the disparate programs. He appointed a genome committee with scientists associated with the various agencies' genome programs.

Japan learned well the lesson brought to its shores by Commodore Perry. Technology was power. The genome project, with one foot planted in technology and the other in pure basic science, was seen in radically different ways by American and Japanese cultures. In the United States, it was conceived as a government-funded public good—an informational resource and the source of new research methods. In Japan, there was ambivalence about how to manage such a project. One group saw the genome project as an opportunity to found science on a Western base, with autonomous science institutions pursuing knowledge for the public good. This group dominated the early genome planning effort. Matsubara noted that in planning the Japanese genome program, "we gave top priority to international collaboration."[26] This ultimately carried over into patent policies for the government-supported projects, although of course the policies pursued by university scientists could not bind their private counterparts. This goal of open science contended with those who would couple biotechnology, and the science related to it, directly to the industrial base and adapt it to corporate interests. As the genome project grew, it was not clear which faction would ultimately prevail.

Policies in the United States and Japan were, in many respects, drifting in opposite directions. In the United States, a relatively small number of administrators in science agencies successfully launched the genome project. In Japan, the ministries vied for dominance without the same pressure for cooperation faced by DOE and NIH in the United States. The resulting effort was more atomized. Bureaucrats with little understanding of the underlying science, or its importance, made more decisions in Japan; and far more of them had to be convinced. Genome research programs in Japan were thus likely to be more independent bureaucratically than the joint NIH-DOE effort. Against this bureaucratic independence, however, was a countervailing trend. The proclivity to rely on very senior scientists with international stature meant there was a limited number of advisers, and they communicated with one another and often sat on advisory committees for several agencies.

In the United States, scientists identified an objective for the genome project and quickly persuaded Congress and federal science agencies to use public resources to attain it. In Japan, the scientists appeared to wield far less direct power over the agencies that funded their work. The federal agencies in the United States controlled the lion's share of funding for basic biology research; in Japan, the anemic government support for basic research left more uncertainty about the future character of genome research. Would it be dominated by academics striving to put Japan atop the world of science, by industrial firms hoping to capture the power of the new biology, by local governments whose relative fiscal health opened the door to a new regionalism in Japan, or by the national ministries that aspired to extend their reach by replicating previous industrial policy successes in electronics and automobiles?

Policy on the genome project confronted uncertainty in several layers. The

connection between genome research and industry was loose, although real. A vigorous and seemingly irresolvable debate centered on whether direct government promotion conferred advantages for international economic competition. And the objectives of national economic policies in the face of large multinational corporations were ambiguous. Congressional patrons of genome research saw the genome project as a vehicle to maintain a technological advantage over Japan.

As the Human Genome Project officially began in October 1990, by Watson's decree, the world of molecular biology was in transition. The dominance of American science was giving way to uncertainty, with feisty bickering among scientists over increasingly intense grant competition and the prospect of a shrinking or constant science funding pie. In Japan, there was much handwringing, and growing consensus about the need to reform science funding. Great confidence in Japan's long-term economic vitality might or might not translate into policies to sustain scientific research. The question was not whether the economic engine was powerful enough, but whether scientists would be allowed into the control room.