PART FOUR

Genome Gone Global

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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.