PART FIVE

Ethical, Legal, and Social Issues

16

A New Social Contract

NANCY SABIN WEXLER radiates openness, integrity, and commitment; she is a doer with a big heart. Her passion for the science of genetics is grounded in personal experience. Her mother, Leonore Sabin Wexler, died of Huntington's disease, as did her uncles Jesse, Seymour, and Paul, and their father, Abraham Sabin (Nancy's maternal grandfather). As Alzheimer's disease did in the Ross family, Huntington's disease cut a wide swath through the Wexler family. Nancy, her sister, Alice, and her father, Milton, watched as Leonore, a woman of formidable intellect, developed uncontrollable movements and deteriorated mentally.

On May 14, 1978, it was over. Her body was cremated, according to her wish. The funeral was strictly family. We spent the time reading letters she had written in the early days of her marriage. They were cheerful, exuberant, and full of intelligence. They recreated the woman who had been vibrant and alive. Now that it was finally over, we could afford to remember her when she was healthy and allow ourselves to feel the enormity of the loss.[1]

When Milton Wexler first discovered the diagnosis in 1968, he called Nancy and Alice home to Los Angeles and explained the prospects. Nancy was in London at the Hampstead Clinic Child Psychoanalytic Training Institute, having just graduated from Radcliffe. She went on to do graduate work in psychology at the University of Michigan, and wrote her dissertation on how

those at risk lived with the threat of Huntington's disease. She then taught for two years at the New School for Social Research in New York City.

Opportunity knocked for Nancy Wexler at age thirty, when she was hired as executive director of the Congressional Commission for the Control of Huntington's Disease and Its Consequences (the Huntington's Commission). The history of the commission is another story of a woman's persistence. After singer Woody Guthrie died of Huntington's disease, his wife, Marjorie, formed the Committee to Combat Huntington's Disease to focus attention on the disease and to lobby for action in Washington. Congress subsequently created the Huntington's Commission, which was housed at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) within the National Institutes of Health (NIH). The commission's task was to recommend what Congress should do to combat Huntington's disease. Milton Wexler had formed the Hereditary Disease Foundation in 1968, to focus on the science,[2–4] and Nancy's expertise and family background made her a logical candidate to direct the commission.

The commission published its report in 1978,[5] and Wexler went to work at NINDS to implement its recommendations. She became the impresario of Huntington's research, enticing the best scientists she could find into the field. It became an American success story, balancing the strengths of the public and private sectors. The Hereditary Disease Foundation was the private arm that could move quickly. It convened a series of informal workshops that would have been more difficult to engineer under federal auspices. NINDS had much deeper pockets, and the infrastructure to cultivate the best science through grants.

In 1979, the Hereditary Disease Foundation held a workshop on applying recombinant DNA technology to search for the Huntington's gene. Alan Tobin, a UCLA researcher and the foundation's scientific director, was convinced that direct study of DNA was the fastest route to solving the problem of Huntington's disease.[3] It seemed farfetched to many,[6] but the idea of a genetic linkage map of the human genome had begun to grow among a small group of cognoscenti. A group in Boston that included David Housman (MIT) and Joseph Martin (Massachusetts General Hospital) was thinking seriously about genetic linkage mapping as part of a nascent Huntington's research center.[3] The Botstein et al. paper was not yet published, but the notion was becoming known, particularly in Boston. Arlene Wyman and Ray White were just beginning work to find the first DNA marker in nearby Worcester, in collaboration with Botstein at MIT.[7,8] Botstein came to the workshop, where he scribbled furiously on the board in a persuasive display of intellectual pyrotechnics. The foundation placed a bet on genetic linkage mapping.

P. Michael Conneally at the University of Indiana searched for linkage between Huntington's disease and protein markers, while a team led by James Gusella began to work with the new DNA markers. Gusella was a graduate

student with David Housman at MIT and later went to work at the new Huntington's Center Without Walls at Massachusetts General Hospital. The NINCDS-sponsored program grew out of the Huntington's Commission recommendations; its NIH project officer turned out to be Nancy Wexler.

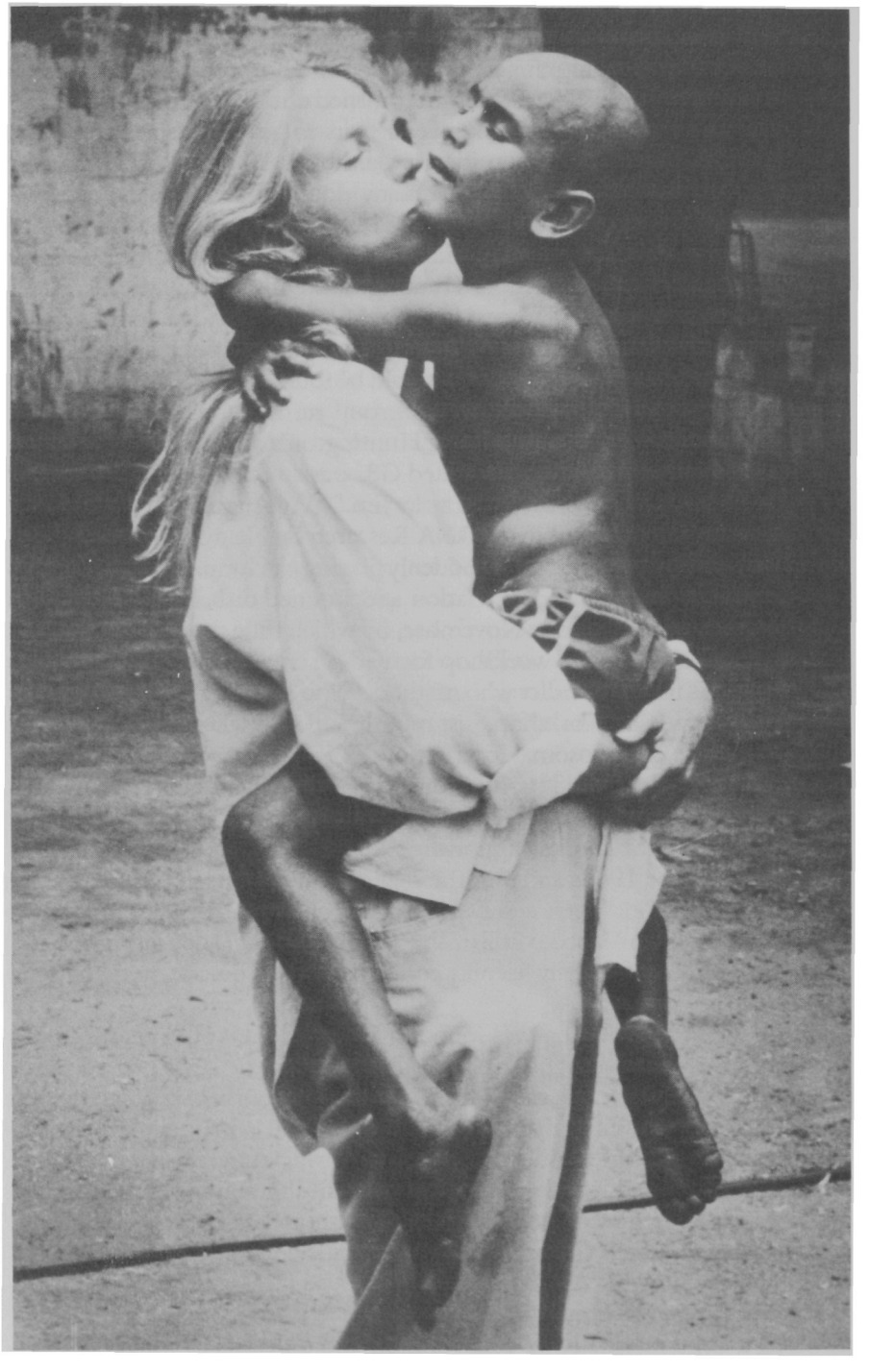
The DNA marker project took several years to get up to speed. By then, the prospects had brightened considerably, although DNA markers had never been used to find disease genes, and many doubted they could be. David Housman and Richard Mulligan chaired a May 1983 workshop convened by the Hereditary Disease Foundation in Cambridge, Massachusetts. The topic was "What Can Be Learned About Huntington's Disease Once the Gene Has Been Located?" According to one report, the meeting ended "on a note of sobriety for the distance to be traveled and genuine offers of assistance some five or ten years hence when a marker would be found."[9] Wrong.

Barely three months later, Gusella's group turned up a promising lead. They found a possible linkage between Huntington's disease and a marker on chromosome 4. This marker, designated G8, was among the first tested.[3;4;10] (Thereafter, Gusella was known as "Lucky Jim."[4]) An August workshop, titled "Clinical Impact of Recombinant DNA Research on Neurogenetic Diseases" and once thought premature, was suddenly playing catch-up.[11] That workshop took place "in an atmosphere of elation and stunned disbelief."[9] The results were published in *Science* that November, by which time the linkage was well established.[12] A November workshop focused on issues that might emerge as the marker was used to predict who might develop Huntington's disease.[11]

At a January 1984 workshop, just months after Gusella and others found the approximate chromosomal location of the Huntington's gene, a consortium of laboratories formed spontaneously to search for the gene itself and the DNA alteration that caused the disease. Wexler and the Hereditary Disease Foundation were the spokes supporting the wheel. The consortium held together through the 1980s and into the 1990s. Other groups outside the consortium—such as Rick Myers and David Cox in San Francisco, Michael Hayden and his coworkers in Vancouver British Columbia, and groups in Europe and Asia—continued in generally friendly competition for a decade, until the gene was found.[3]

Once the gene's location was found, many hoped it would be only a few years until the gene were found. The hunt for the gene itself proved much more arduous. It took a decade of dedicated work, but Gusella's group did lead the effort that eventually uncovered the gene and the nature of the mutation causing Huntington's disease.[13] The gene was more elusive than some because it was embedded in a complex and confusing region. In the end, the article announcing the end of the search was authored by the entire Huntington's Disease Research Group, which by then included fifty-eight authors in six groups spanning the Atlantic.

The hunt for the Huntington's disease gene was far more than luck. It involved a large international collaboration and a decade of intensive work



with many false starts. Another critical factor was the discovery of a large family with Huntington's disease living near Lake Maracaibo in Venezuela. This family had been discovered by a Venezuelan physician, Americo Negrette. Wexler flew down to investigate in 1979. It turned out to be an enormous pedigree, containing thousands of living members, with an immense toll of Huntington's disease. Thus began an annual rite of visitation that continues to this day. Wexler became a local fixture, known as La Catira ("the Blonde"), and the Venezuelan families became an extension of Wexler's family—a group with whom she shared an emotional bond deepened by mutual suffering and the fierce struggle against a common enemy.[2] Dr. Negrette described the feeling of working among the Maracaibo families in the company of La Catira:

> I arrived in their homes and their shacks, and left feeling destroyed inside because I felt incapable of solving the problems. . . . At times I would distance myself from them—for years. . . . and feel guilty. But now as I grow older I have become more sensitive to the pain of others. So much so that it now no longer feels apart. It is my pain, this pain that they feel. And it is for this that I love La Catira. Because she comes every year, for more than ten years to battle. . . . She brings them medicines and she brings them projects for their social welfare. But she brings them something more precious yet. She brings them an immeasurable love. She pours on them a warm contagious care. I have seen her embracing women and embracing men and kissing children. Without theater, without simulation, without pose. With a tenderness that jumps from her eyes. And her fingers are claws of love mingling with tenderness and passion. . . . I adore La Catira who has as hair a hanging waterfall of gold. Like the love she gives.[14]

The new ability to detect Huntington's disease, particularly in the decade between finding the gene's chromosomal location and discovering the gene itself; brought complex medical, family, and social choices. Who would take the test? Who *should* take the test? Who should offer it, and under what conditions? How could the quality of laboratory work be assured? How much counseling should be required before administering the test? Who other than individuals and their physicians should have access to test results? Should information about Huntington's disease in one individual that was relevant to another be communicated without knowledge of, or over the objection of, the person tested? If so, under what conditions and how? These questions had long been debated, but in the abstract. In 1983, technology called everyone's bluff. The stakes were very high—life itself. The game was, in Nancy Wexler's words, "genetic Russian roulette."[15]

When the test became available, the questions that had been merely rhetor-

---

Nancy Wexler, a leader in the search for the genetic basis of Huntington's disease (and herself a member of a family affected by the disease), was picked to head the NIH group devoted to exploring the ethical, legal, and social implications (ELSI) of human genome research. She is shown here with a young Huntington's patient, a member of a large family with the disease living near Lake Maracaibo in Venezuela. *Peter Ginter photo, courtesy Nancy Wexler*

ical suddenly became urgent and real. Some of the answers were surprising. Nancy had always assumed she would want to know; she would therefore take the test. But Milton Wexler pointed out that it was not entirely an individual decision. The family was being tested, and if both Nancy and Alice took the test, the chances were three in four that one or both of them would turn out to have the Huntington's gene.[2] If either had the gene, all three Wexlers would be crushed. Did they really want to know? Taking the test required more thought. Wexler asked herself:

> Would I change my job? No, I love what I'm doing. Would I work any less? No. Would I work any more? I'm not sure I can. Would I be any less frantic and obsessional? Probably not. Would it change personal relationships and friendships? No. There's an awful lot it wouldn't change. . . . I'm already happy, how much happier am I going to be? Part of me realized how happy I am, being part of this whole research process that's going to make a difference in the future.[16]

Even disclosing whether she had taken the test or not was an issue. Wexler was a highly public figure, but why should the public know about her private decision? She wanted to make clear that she might take the test or she might not. She believed it was a matter of personal and family choice, not a matter of public record.[17]

The technology of genetic testing replaced implacable fate with agonizing choice. A majority of those eligible to take the test end up not doing so after counseling. Those who opt in favor of testing face a difficult psychological travail, whether the results show the Huntington's gene to be present,[18] or absent,[19] or prove inconclusive.[20] The first empirical study of the benefit of predictive testing for Huntington's disease suggested that those who discovered they were at decreased risk fared better on psychological measures of distress soon after testing than those whose risk status was unchanged—those who chose not to be tested or for whom the test was inconclusive. After a year, both those who learned of increased risk of Huntington's and those with decreased risk scored better, suggesting that even bad news with increased certainty might be perceived as better than lingering uncertainty.[21] The tests might indeed provide a psychological benefit, but the complexities of family testing nonetheless still demanded care and caution.[22] The control group in the study combined those who deliberately chose not to have the test with those who had it but did not get conclusive results, which would intuitively seem to be very different psychological situations. While the first study was encouraging, therefore, this was not a green light so much as a flashing yellow one.

Producing a diagnostic test was not the purpose of locating the gene; it was a side effect. The ability to use DNA markers to predict Huntington's disease was, in Wexler's words,

> a way-station on a more important journey: the isolation and sequencing of the HD gene with the aim of treating the gene or its consequences. . . . If the initial steps on the

road to finding treatment can be of clinical use for presymptomatic and prenatal detection for some at risk, so much the better, but the fact that the HD gene now has a chromosomal localization will hopefully speed the day when effective treatment can be offered to all families.[9]

Wexler's charm and warmth enclosed a powerful engine of change. Her passionate devotion to genetics was born of seeing it as the sole salvation for herself, or at least for future individuals facing the same gruesome choices. Knowledge might or might not yield power; but ignorance was certain impotence. Hers was a smooth and almost imperceptible style of exercising great power. Huntington's disease may have stolen Nancy Wexler's mother, but it also gave her life a meaning it might not have found otherwise: "The struggle against hereditary disease has given me purpose and direction."[1] She has shared this wealth.

The decision to commence a program to anticipate the social implications of genome research was made by James D. Watson alone, without conferring with anyone else at NIH. It was one of Watson's first acts on joining NIH. "Some very real dilemmas exist already about the privacy of DNA. The problems are with us now, independent of the genome program, but they will be associated with it. We should devote real money to discussing these issues. People are afraid of genetic knowledge instead of seeing it as an opportunity."[23] Watson thought NIH should set aside 3 percent or so of its genome funds for this purpose.[24] He argued that the genome project was "completely correct" to go after gene maps and DNA sequence data as fast as possible, but it was essential to be completely candid about how such information could be abused and to suggest laws to prevent such abuse, because "we certainly don't want to mislead Congress."[25]

Having made a commitment as his first public act, Watson then had to carry it out. He officially assumed his NIH associate director position on October 1, 1988. Three weeks later, the first major international meeting on genome research took place in Valencia, Spain. Organizer Santiago Grisolía had achieved his goals of a high-profile meeting by attracting Nobelists Christian Anfinsen, Hamilton Smith, Jean Dausset, and Severo Ochoa, as well as Watson. Victor McKusick, James Wyngaarden (still NIH director), and many other prominent scientists joined this star-studded cast of scientific heavyweights in October 1988 at the Hotel Sidi Soler along the Mediterranean coast. The meeting had an unexpected benefit. Watson had just begun his NIH duties and was nearing completion of the list of outside advisers to appoint. Nancy Wexler was at the meeting to discuss medical applications of genome research, which were still only a sideshow in the genome debate, in a period when most discussion centered on cost and scientific strategy.

At one of the sumptuous Valencian meals, Wexler found herself in the company of Wyngaarden, Watson, McKusick, and several others while they discussed who should represent human genetics on the advisory committee.

Wexler was, of course, an ideal candidate—as a psychologist, a person at risk of genetic disease, a fieldworker on pedigree research, and someone intimately familiar with the science. The initial interest in appointing Wexler came less from her interests in ethical and social issues than from her ability to balance the scientific background of the advisers with a broader view of human genetics. When the NIH Program Advisory Committee on Human Genome Research broke into working groups, however, it was obvious that one group had to concentrate on ethics, law, and social policy. Nancy Wexler alone among the advisers had standing to chair such a group. She and McKusick were both appointed, and she was designated chair of a working group on ethical, legal, and social implications (ELSI) of human genome research.

Congress had signaled concerns about ethical issues even earlier, as genome plans first surfaced. In 1986, Edwin Froelich, physician adviser to Senator Orrin Hatch, called Charles DeLisi to his office, soon after having learned of the Department of Energy schemes for a genome project. Senator Hatch was the ranking Republican in the Committee on Labor and Human Resources. The committee had jurisdiction over NIH, but not DOE. Froelich nonetheless expressed grave concern to DeLisi that DOE's genome research should be scrutinized for its broader impact, particularly whether it would lead to more prenatal diagnosis and abortion. Froelich also called Ruth Kirschstein, director of the NIH institute central to genome research planning, when he heard of NIH's emerging interest in 1987. Kirschstein and W. French Anderson went down from Bethesda to Capitol Hill to assure Froelich that NIH was indeed concerned about these matters. Froelich wanted explicit attention to ethical issues, or the human genetics program would be in jeopardy.

When we learned of these concerns at OTA, we relayed them to Chase Peterson, president of the University of Utah and a member of OTA's overall advisory committee. In addition, I called Ray White, whose genetic linkage group at the University of Utah was becoming a world hub of human genetics—one of Utah's most conspicuous intellectual landmarks. Peterson met with Hatch's staff to help clarify the importance of genome research in Hatch's home state.

Meanwhile, John C. Fletcher, chief of the bioethics program in the NIH clinical center, wrote a memo to Kirschstein expressing concern that "the NIH should not appear to be driven by a technological imperative. . . . Are we as concerned about preparing society to find the wisdom to live with a control of this new knowledge as we are with seeking the knowledge? I hope so, but those who work on the proposal need to have a plan to examine the issues."[26]

Independent of these activities, Senator Barbara Mikulski of Maryland met with me on June 15, 1988, to express her concern that "go-go" science would race far in advance of prudent policies. It could become difficult to contain its adverse impact on individuals and society. Enthusiasm for the biology needed to be tempered by a public policy process to anticipate its social impact. As the

NIH authorization bill went through the Labor and Human Resources Committee in the Senate that fall, Senator Mikulski again raised this concern. Senator Edward Kennedy, the committee chair, echoed it, and noted his long support for the National Commission and President's Commission (previous bioethics commissions), and his hopes for the congressional Biomedical Ethics Board, of which he was a member. These meetings about the social, legal, and ethical implications of genome research, however, were for the most part hidden from public sight and only tangentially related to planning at NIH and DOE until late 1989.

The American ELSI program was unfocused as it began. The first announcement of the NIH grant program asked five general questions: "What are the concerns to society and to individuals arising from the Human Genome Project? What specific questions in the broad area of ethics and law need to be addressed? What can we learn from precedents? What are possible policy alternatives and the pros and cons of each? How can we inform and involve the public and stimulate broad discussion?"[27] The response to this somewhat vague solicitation was understandably diffuse and general. Bettie Graham, acting administrator of the ELSI grants program until a permanent staff person could be hired, noted: "We have very little experience in the area and we need a point of reference."[28] Many of the first grant applications were to host conferences that would consider all the issues. Ten such conferences were eventually funded that first year.[29]

Nancy Wexler's ELSI working group met in September 1989, to set forth a series of objectives for the program. It was the first meeting of the group and led directly to a refinement of the program announcement to guide those seeking grants. The five general questions became five pages of background and a series of nine topic areas, ranging from immediate policy questions—fairness in use of genetic-test results in employment and insurance—to philosophical issues—how conceptions of personal identity and responsibility might change in light of new genetic knowledge.[30]

Wexler proposed activity along several fronts. She wanted to hold a series of small workshops with the working group, as well as larger town meetings to solicit broader input. The working group would also continue to help steer the research program of grants and contracts. What more the ELSI group should do was open to debate, particularly whether the group should become a forum for policy deliberations. Questions about how far the ELSI group should go into policy analysis surfaced repeatedly at meetings in February and September 1990 and January 1991. The working group took its cues less from internal debate, however, than from events swirling about the genome program.

Congressman David Obey forced NIH's hand in hearings on the 1991 budget. He had a long exchange with Watson, expressing his view that genome research might best be delayed until prospects for protecting genetic

information were better.[31] He followed up by inserting report language that mandated a program to devise policy options to thwart adverse uses of genetic testing, and made explicit the need for a more activist approach.[32] Obey thus tilted the balance in favor of the more activist members, among whom I counted myself.

The ELSI group worked on several issues simultaneously. It was composed of a core group with a long-standing interest in the social uses of genetics. Tom Murray, head of the bioethics program at Case Western Reserve and long associated with genetic-testing issues through work at the Hastings Center in New York and then at the University of Texas, prepared an overview of issues.[33] Jonathan Beckwith of Harvard Medical School had helped to isolate the first bacterial gene and later was involved in the recombinant DNA debate of the mid-1970s. He was a prominent antagonist in a controversy over whether males with an extra Y chromosome were more prone to criminal behavior, and had been a vocal skeptic of claims that IQ was genetic.[34] Tom Murray and Beckwith cochaired the insurance task force under ELSI. Robert Murray, a clinical geneticist from Howard University who had direct experience with the problems of sickle-cell-screening programs of the 1970s, agreed to oversee activities related to the introduction of genetic tests into medical practice. Patricia King was a law professor with extensive policy background. She had served on the recombinant DNA advisory committee and on both the major federal bioethics commissions. Victor McKusick was, of course, the dean of human genetics, and also chairman of the Human Genome Organization's ethics committee until mid-1991. I was the youngster, on the group for its first meeting, off for the second (because I was working as a consultant to NIH), and then back on again after leaving NIH employ. I was chosen for my background on the Hill, where I had written OTA reports on gene therapy and the genome project, and for my experience as acting director of a congressional bioethics commission, the Biomedical Ethics Advisory Committee.

The ELSI program at NIH got a major boost when Elke Jordan hired Eric Juengst to direct it. Eric had a Ph.D. in philosophy from Georgetown University, where he worked on issues related to bioethics. He subsequently worked at two other major bioethics centers before joining NIH—at the University of California, San Francisco, and the Hershey Medical Center in Pennsylvania. Juengst brought a broad background in the history of biology, philosophy, and pragmatic bioethics to NIH, and he had previous experience as an administrator at the National Endowment for the Humanities to boot. Eric had twin responsibilities—to help the ELSI working group formulate policy and also to administer the NIH portion of the ELSI grants program.

Michael Yesley, a lawyer, joined the ELSI working group at its third meeting. During the mid-1970s, Yesley worked at NIH, where he was executive director of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the nation's first federal bioethics commission. He then went into consulting work and eventually to Los Alamos

National Laboratory. When the DOE program moved into bioethics, he was already working for Los Alamos, and he became a logical point man for DOE interests.

Nancy Wexler decided to structure the effort by keeping the working group small, but supplementing its expertise at a series of workshops on different topics. Outside experts could be brought in at each meeting. Juengst had line authority over the NIH grants program, for which the ELSI working group would serve as a steering committee. Oversight of DOE grants fell to Michael Yesley as a consultant, and DOE line staff in the Germantown headquarters. After the first round of DOE "ethics" grants, Daniel Drell became the principal DOE staff person.

The grant mechanism supported conferences and outreach, with large "town meetings" planned later. By the end of its first year, the genome office was supporting sixteen projects extramurally, through grants and contracts. These ranged from small conference grants, to an Institute of Medicine study of genetic testing in clinical practice, to substantial funding for public education that included a Public Broadcasting Corporation production, *The Future of Medicine*.[35] By September 1991, NCHGR had funded twenty-five extramural grants and ten national conferences.[29] The five vague questions of March 1989 had grown into a ten-page strategic plan for Congress[36] and a growing portfolio of projects supported throughout the nation.

The program attracted some attention from other NIH centers and institutes that had contemplated programs in social and ethical issues before, and now had an experiment to observe. The National Cancer Institute, National Institute of Neurological Disorders and Stroke, and National Institute of Child Health and Human Development watched closely. When Bernadine Healy came in as the new NIH director in mid-1991, she commenced a major strategic planning exercise for the institution. Attention to ethical and social issues became a part of this planning exercise, and Juengst emerged as the NIH staff person with the most direct experience, taking the lead in preparing the strategic planning documents on social, legal, and ethical issues in biomedical research.[37] He thus became one of the principal architects of the NIH-wide proposal to address such issues.

One potentially adverse effect of the ELSI genome program was the concentration of resources in a relatively narrow field of biomedical research. As support for bioethics related to the genome project grew, and with few resources available for other lines of bioethical analysis, many bioethics programs developed modules on genetics. This may have helped achieve the goals of the genome office, but it also skewed concern with bioethics toward the genome research. Where cash went, ethics followed.

Nancy Wexler personally took the lead on efforts to encourage field trials of genetic testing for cystic fibrosis (CF). In late 1989, this was emerging as the most urgent policy problem related to genetics. It began with discovery of

the CF gene,[38–40] a great technical triumph. It turned out, however, that CF testing would be far more complex than expected. The CF gene encoded a membrane protein regulating the transit of chloride ions across cell membranes, and the cellular defect could be corrected by inserting the normal gene.[41] The gene's DNA sequence, however, was marred by a staggering array of different mutations in different patients. One common mutation, the loss of three base pairs, accounted for the majority of cases in most populations. Scores of different mutations were also associated with the disease, however, making impractical a simple DNA test to detect them all, at least until new technologies developed.[42] DNA sequencing might disclose the full range of mutations, but sequencing remained for the time being too expensive and too slow for routine clinical testing.

Different population groups varied widely in the relative frequency and diversity of CF mutations. In northern Yugoslavia (still a single country at the time), the three-base-pair-deletion mutation accounted for only 26 percent of CF genes, compared to 88 percent in Denmark. In North American groups, the range went from 3 percent (among those of Eastern European Jewish background) to 84 percent (in a mainly Caucasian group).[43]

Genetic complexity in populations was further confounded by clinical heterogeneity. The disease varied in severity and range of symptoms. Most symptoms stemmed from viscous mucus that plugged duct systems in the lungs and pancreas. Lung plugs sealed off pockets that became breeding grounds for recurrent infections. Clogged pancreatic ducts obstructed the secretion of digestive enzymes into the intestines, so that foodstuffs were poorly digested and absorbed. The life span of CF patients soared in the 1970s and 1980s, with better antibiotic treatments and supplementation with digestive enzymes. CF children in the past had generally died before age twenty, but now most lived well into their twenties and even beyond. With CF, judgment of clinical severity was more uncertain, in contrast to other unequivocally horrid genetic diseases such as Tay-Sachs, in which infants begin to die even as they are born. Everything about CF was more complicated than previous genetic diseases, and yet it was far more prevalent in the American population.

Testing for the most common mutation would pick up, on average, about 70 percent of carriers with a single copy of the CF gene. It would thus miss the 30 percent of potential CF genes caused by other mutations. If two prospective parents were both carriers, each of their children had a one-in-four chance of developing the disease. Having one CF gene did not cause the disease, but if both copies were defective, disease inevitably ensued. The problem was that the test would miss many CF carriers, and so many couples would not be aided by the test.

The unanticipated diversity of mutations immensely complicated the process of testing individual patients and screening populations for CF. A poll in England taken just before the gene was discovered found that 80 percent of those who had heard of CF wanted to know if they were carriers.[44] That desire

for a test confronted considerable technical and logistical obstacles. There was fear in the United States that profit incentives for private testing laboratories would combine with fear of malpractice to unleash a massive wave of CF testing. If physicians did not offer the test, they could be sued. Yet interpreting test results for CF was even more complicated than for most other genetic diseases, which were already hard to explain. Genetic counseling and other genetic services were strained even without a massive increase in demand.[45] The existing CF tests would add many new clients, a substantial fraction of whom would require lengthy counseling to understand the disease and the meaning of equivocal test results.[45;46]

The American Society of Human Genetics adopted a statement at its annual meeting on November 13, 1989, hoping to stave off premature population screening. The society endorsed CF testing for those who had a close relative with CF, but indicated population screening would become practical only when the test was far more sensitive. Genetic testing for CF was a research topic and an adjunct to individual genetic counseling, not a standard of medical practice.[47] The statement was intended to thwart malpractice suits and to apply a moral brake to private laboratories promoting CF testing.

In March 1990, an NIH workshop on population screening concurred that population screening should not be undertaken until the tests detected a much higher fraction of total CF genes and until the medical care system was much better prepared.[48] The Office of Technology Assessment commenced a study of CF testing later that year.[49] The public statements were expressions of consensus, not unanimity, and they referred mainly to the American health care delivery system. A review of the arguments for and against wide use of CF testing,[50] published in the *American Journal of Human Genetics,* found strong arguments on both sides. In the United Kingdom, Canada, and Denmark, testing programs went forward.[42] In the United States, CF testing programs became a focus of controversy, sparked by the disarray of health-care financing and fueled by the vitriolic abortion debate.

Among clinical geneticists, concern shifted quickly from stemming the tide of genetic testing to analyzing how a CF test might best be introduced into practice. The American Society of Human Genetics indicated a need to evaluate pilot testing programs.[47] The NIH statement was even stronger: "Pilot programs investigating research questions in the delivery of population-based screening for cystic fibrosis carriers are urgently needed."[48] The need may have been urgent, but there was no eager patron. The Cystic Fibrosis Foundation, which had sponsored research to find the gene and was now funding work to understand how the gene led to disease, saw its mission as research, not test development and genetic services. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) viewed the problem similarly, at least initially. A focus on biomedical research, narrowly defined to exclude research on health services, became the public rationale for inaction.

Another rationale, voiced privately, was a judgment of political risk. The

coalition supporting CF research might fracture over the abortion issue.[51] This would severely hamper the research efforts at both NIH and the CF Foundation. Pilot testing meant mostly testing for carriers. That was fine, but the problem came further down the line. The primary reason to test most carriers was to inform them about reproductive choices. If both parents were carriers, they stood a one-in-four chance of having a child with CF in each pregnancy. They could choose not to have children, to seek artificial insemination, or to take their chances and have children. If a fetus tested positive for CF, some families would clearly carry on the pregnancy, judging the disease insufficiently severe to merit abortion. Other families, however, would choose to abort.

With sustained research the primary objective, divisive debate about CF testing and abortion could only undermine political support. The power of this fear was exemplified in the NIDDK call for Small Business Innovation Research grant applications. NIDDK sought companies to prepare educational materials for those entering screening programs "about the risks, benefits, and limitations of the test and helping people found to be carriers of the cystic fibrosis gene defect interpret and understand the test results." A final caveat made this laudable exercise a charade: "The scope of this topic does not include materials related to reproductive decisions."[52] Companies could take the horse to water, but not let it drink.

One proposal for a CF testing pilot program came to NIH during this period, but it was raked over the coals by incompetent peer review.[53] The proposal made the mistake of technological optimism, asserting that 95 percent of CF mutations would be identified within a year. In the lag between submission of the proposal in January 1990 and peer review in June, the conventional wisdom changed. The optimism that all CF genes would be identified quickly that held sway immediately after the gene was identified gave way to recognition that the task was more formidable. The urgency of pilot programs did not hinge on finding 95 percent of mutations, and it was a mistake to make the claim. This red herring, however, is not what doomed the proposal, as the peer review statement made quite clear.

The peer reviewers believed a more serious weakness of the proposal was that nothing more could be learned from the pilot project. The relevant information was already known. The review sheet opined it was "not clear that it [the pilot project] will uncover new and significant information not already available from previous population studies involving other genetic diseases such as hemoglobinopathies and Tay-Sachs."[54] The study section thus judged that the proposed study would turn up little useful new information.

This errant judgment failed to account for vast differences between those diseases and CF, different technical uncertainties of the genetic test, and changes in genetic services in the intervening decade. CF testing and screening would have to be entirely different from previous programs for sickle-cell anemia, thalassemia, and Tay-Sachs disease. CF was more clinically variable than Tay-Sachs; the size of the population at risk was ten times larger, and the disease

affected those of Caucasian descent, raising a completely different set of social issues related to ethnicity, economic status, and educational background. Federal support for genetic services over the previous decade had atrophied, and public health programs in the states were retrenching. The shifts in the delivery of health-care services, the technical basis of the tests, and the complexity of interpreting test results overwhelmed any similarities to previous experience in genetic testing, but the peer reviewers were mainly laboratory geneticists unfamiliar with the wider problems confronting genetic services. A few lonely voices dissented from the majority, but their votes could not raise the priority score to a fundable level or change the consensus against the pilot project.[55] It was as if the study section were to decline to study a gene for prostate cancer because someone had found the one for breast cancer a decade earlier.

Based on this shoddy evaluation, the NIDDK council passed over the only pilot testing project under review in fall 1990. NIH's inaction frustrated clinical geneticists, who began to raise a ruckus.[51] Nancy Wexler courageously steered the ELSI working group straight into the storm.

Wexler's ELSI working group was just catching its stride as the CF controversy hit. The working group became a natural forum because of its composition and, more to the point, because it was the only conspicuous place to discuss the pressing policy issues in the federal government. Virtually all the working members had long been involved in public policy regarding genetic testing. They were keenly aware that CF was at once the single most common recessive single gene defect in the American population and also the prototype for a long list of genetic tests to be developed over the ensuing decade. At a gathering in Williamsburg, Virginia, in February 1990, the working group identified CF testing as a priority item. An NIH workshop on CF screening was held in March, cosponsored by NIDDK and the genome center. The ELSI working group held another, smaller meeting of CF experts from the United States, the United Kingdom, and Denmark in September 1990, and prepared a summary statement that stressed again the urgent need for action by NIH and a sense of growing frustration among medical geneticists.[42]

When stories appeared about disgruntlement in the wake of that year's annual meeting of the American Society of Human Genetics in Cincinnati, the timing was right. In a background paper for the ELSI group, Benjamin Wilfond and Norman Fost of the University of Wisconsin further substantiated the need for greater attention to policy analysis before large-scale screening programs were put in place.[46] Nancy Wexler presented the ELSI working group's summary statement to the NIH's genome advisory committee in December. The genome advisory committee was leery of getting involved in clinical work, fearing it would create an expectation that the genome office would support field trials of every genetic test developed thereafter. The committee agreed, however, that CF pilot tests were just too important, and the genome center should take the lead if other institutes did not.[56] The full

committee endorsed the statement, and urged NCHGR to "take a leadership role in developing support for well designed, cost effective pilot research projects." The genome advisory committee petitioned Watson to pursue support from other parts of NIH and other agencies.[57]

After the meeting, Elke Jordan and Eric Juengst met with acting NIH director William Raub. Raub was supportive, and convened a working group of several institutes. On January 31, 1991, a group of advisers met with staff from the genome office, NIDDK, and the National Institute of Child Health and Human Development to help prepare a request for applications on cystic fibrosis.[58] This led to a request for applications for pilot CF testing, with the genome center taking the lead. NCHGR issued the call and managed review of more than thirty applications.[59;60] Seven grants were given to six centers to study various approaches to CF testing.[61]

In the CF story, the ELSI working group provided a fulcrum for moving the NIH bureaucracy toward pilot testing. By serving as a forum for discussion linked to but independent of NIH (working group members were not NIH staff), the group became a mechanism to reason toward solutions. Once the genome center made a commitment to pilot projects, other institutes followed. It was an early victory for the program, showing it could have an impact.

The ELSI program exemplified how the foundation of science was broadening. Taxpayers funded the lion's share of basic science, and science intruded ever deeper into daily life, working its way into public consciousness. Science was weaving itself more tightly into the social fabric. Where science was once a cultural embellishment, a luxury for affluent cultures and a hobby for upper-crust patrons, in the post–World War II period it had become the engine for technological change. Technology, for its part, was a major cause of social transformation. The rules had to change. It was no longer sufficient to recount Vannevar Bush's paean to "Science, the Endless Frontier," echoed though the years since he coined the phrase in 1945.[62;63]

Daniel Koshland, editor of *Science,* wrote an editorial that stood foursquare behind the genome project, invoking the promised benefits of preventing diseases by understanding their genetic causes. He gave special emphasis to mental illness:

> The costs of mental illness, the difficult civil liberties problems they cause, the pain to the individual, all cry out for an early solution that involves prevention, not caretaking. To continue the current warehousing or neglect of these people, many of whom are in the ranks of the homeless, is the equivalent of providing iron lungs to polio victims at the expense of working on a vaccine.[64]

The National Foundation for Infantile Paralysis (March of Dimes) had faced precisely this dilemma four decades before. It sensibly opted for iron lungs until the prospects of a successful vaccine looked promising enough to shift resources toward prevention.[65] Faith in science bore fruit in one of the

spectacular medical successes of its day—the polio vaccine—but the causal links from poliovirus to poliomyelitis were far simpler and more direct than the connections from genes to homelessness. For disorders clearly involving many genes and complex interactions between person and environment, there were many more opportunities for wrong turns 'twixt gene and effect. Koshland was asking the public to make a leap longer than most were comfortable making. He might well take such leaps of faith; but most Americans seemed inclined to check the landing zone first. Could a Senator Koshland garner votes on a platform espousing "genes for the homeless"? He just might lose, even in Berkeley.

There was nonetheless a kernel of truth in Koshland's rhetoric. Understanding can contribute to the alleviation of human suffering. If genetics helps to clarify the biology of schizophrenia, manic-depressive disorder, and other severe mental illness, it may indeed reduce the number of homeless people by reducing disability. In the near term, however, dissecting genetic factors is more likely to succeed for families like the Wexlers, the Rosses, or the countless others ravaged by genetic diseases traced to one or a few genes. Uncovering genetic factors can also dramatically advance the analysis of risk factors. Families prone to colonic polyps or skin cancers, for example, reveal the weak links in cellular physiology that can lead to cancer. The genetics of familial cancers not only sheds light on the cancers in those families, often providing a welcome technological means to prevent cancer, but also illuminates the general process by which cancer develops in other patients. Knowledge is power. Genetics is the fast track to knowledge, even if it does not run a direct course from a gene to homelessness.

The discovery of new facts, new theories, and new conceptions of the world remains a powerful motivating force for those in science, but does not fully explain the resources devoted to research, both public and private. Science retains its prestige and power to excite cultural pride, but it is also an investment. Biomedical research is regarded as the down payment on future health. Americans are unusually lavish in support of biomedical research, perhaps reflecting a national optimism about the benefits of technology. Today's science is tomorrow's cure or prevention.

The increased scale of the biomedical research, however, carries with it a tendency to self-perpetuation and defensiveness. As the genome program was being formulated, another major theme of biomedical research was the deliberate warping of science for personal benefit—fraud and misconduct. A populist element has expressed skepticism of scientist's motivations, and sees scientists as cold and arrogant fact-seekers oblivious and unaccountable to the world around them, and corrupted by the new-found allures of wealth. A powerful elitist band of scientists indeed has pooh-poohed public controversy over science fraud and misconduct and has seriously underestimated concern for animal rights and protection of human subjects. Between Luddites on one side and arrogant scientists on the other lies a legion of investigators trying to

conquer disease, but also concerned about social harms that might result from their technology. Federal sponsorship of bioethics is intended to foster work in this area.

Biotechnology excites awe and distrust. Genetics inspires wonder at its power, but provokes fear of misuse. Inchoate discomfiture is grounded in a sense that genes are inherently important. Genes are tightly linked not only to other genes, but also to personal identity. It is distressing to contemplate losing control over something so intuitively private, something as close to the self as one's genes.

As Patricia King once noted, "we, the public, worry about human control over nature. We are concerned, for example, that advances in genetics will change the nature of humankind, that we will change the genetic structure of human beings." She went on to observe:

> The policy community has been making policy on a range of issues for a very long time and is comfortable with itself. It is the scientific community that has the most at stake, and it is going to be charged with educating the rest of us about its needs, its methodologies, its frameworks, and its values. It seems to me that the burden rests on the scientific and medical communities to educate people like me.[66]

The programs to analyze the social implications of genome research were a means of dealing with public concerns. Scientists did not want those concerns to obstruct science. For some, the ELSI program and its foreign counterparts appeared to be political preemptive strikes intended to thwart criticism of science. Motives matter, and many read the politics as Watson's ploy to protect his research budget. If it was, it was a ploy that could well backfire. It provided an opening for the program's critics by funding social science that could well turn up issues that genome scientists would find uncomfortable. Indeed, that was one of its mandates. Watson's position was consistent with his past actions. In the early 1970s, Watson was almost alone among scientists in supporting a commission on reproductive technology and new biomedical advances. The Senate had a hard time finding a scientist who did not regard such commissions as intrusions onto sacred scientific lands, but Watson spoke out in favor of public deliberation.[67] If there was a protective motive for Watson's support, there was also a long-standing interest.

The ELSI program was not a shield for scientific miscreants. It was an attempt to articulate the values that should govern the research, and to anticipate adverse social consequences of science in time to avert them. The remarkable feature of the ELSI program—and its counterparts in the EC, French, Canadian, German, Russian, and Japanese programs—was not that they came into being, but how quickly policymakers accepted them as the norm despite their absence everywhere else in science. No comparable movement had seized the imagination since the debates about human research subjects and recombinant DNA technology commanded public attention twenty years before.

The ELSI research program was a welcome addition to the NIH, but even as it successfully guided NIH toward a more rational research program related to CF testing, it also faced deeper questions with social implications well beyond its capacity to manage. Many touched on disparate views of political philosophy, justice, and moral values. The genome project attracted the attention of scholars outside of molecular biology, who then began to scrutinize the directions within science and the broader social context within which human genetics was practiced.

The early history of genetics, particularly human genetics, was imbued with an optimism that genetic factors could explain socially important individual traits, such as intelligence, criminal tendencies, and athletic prowess. The eugenics movement was inextricably woven into human genetics, its most public aspect, as eugenics advocates played a role in public policies on immigration, interracial marriage, and mandatory sterilization.[68] Restrictions on U.S. immigration policy during the 1920s, were perhaps driven as much by ethnic politics as by science, but the testimony of eugenicists was avidly sought. They pointed to correlations between low scores on IQ tests, then just coming into use, and the geographic origin of population groups. Data from the 1920s claimed to show Jews were intellectually inferior, for example, yet decades later, it was an article of faith that American Jews did better on standardized tests.[69] The explanation for low scores in the 1920s was genetic; for superior performance in the 1950s and 1960s, cultural and educational. The resort to genetic explanations seemed to depend on more than just the test results or population clusters; it depended as well on an overlay of largely unexamined social theory. The eugenics movement achieved its zenith in the United States in the 1927 Supreme Court decision on *Buck* v. *Bell,* in which Justice Oliver Wendell Holmes justified the mandatory sterilization of Carrie Buck by declaring "three generations of imbeciles are enough."[70]

This decision, like many eugenic initiatives, was based on faulty evidence and ideology masquerading as science. A factual retracing of the case suggests that Carrie Buck was raped by the son of the family for whom she worked, and was remanded to an institution, the same one in which her mother and sister resided, when she became pregnant. Despite expert testimony from some nationally prominent "experts," there is no evidence that she was feeble-minded, and she married twice and lived an unremarkable life after release from the institution. Her mother and sister were also sterilized. Her daughter Vivian, the supposed third generation of "imbeciles," became an honor student before dying in late childhood.[71]

In other nations, eugenics grasped policy with even greater force. In its most infamous embodiment, Nazi eugenics began with the sterilization and then "euthanasia" of those in psychiatric facilities. It then adopted racial overtones culminating in the Holocaust.[72–78] Physicians and geneticists played an active role in promoting the ideology of racial hygiene.[75–78]

Genetic explanation could produce tragic consequences when its reach exceeded its grasp. Evelyn Fox Keller, professor of rhetoric at Berkeley and a historian of genetics, pointed to this tendency in contemporary discourse about molecular biology:

> Without doubt, the 1970s was a decade of extraordinary expansion for molecular biology: technically, institutionally, culturally, and economically. My aim is not to question that expansion *per se,* but rather to question the conventional understanding. . . . The concept of genetic disease, enthusiastically appropriated by the medical sciences for complex institutional and economic reasons, represents an expansion of molecular biology far beyond its technical successes. . . . Today we are being told—and judging from media accounts, we are apparently coming to believe—that what makes us human is our genes. Indeed, the very notion of "culture" as distinct from "biology" seems to have vanished.[79]

In his 1991 book *Backdoor to Eugenics,* Berkeley sociologist Troy Duster noted:

> It is the halo from the molecular work of the last decades that has helped provide new legitimacy to the old claimants. . . . Those making the claims about the genetic component of an array of behaviors and conditions (crime, mental illness, alcoholism, gender relations, intelligence) come from a wide range of disciplines, tenuously united under a banner of an increased role for the explanatory power of genetics. Relatively few of these claims come from molecular genetics.[69]

The elucidation of genetic mechanisms for specific diseases loaded a layer of race on top of medical genetics. Population groups of different geographic origin, it was argued, are disproportionately prone to some genetic diseases; hemoglobin disorders are more common among those of African, Mediterranean, or Southeast Asian descent; Tay-Sachs disease is more prevalent among Eastern European Jews. These differences can therefore be traced to mutations passed from generation to generation, and only slowly dissipated through intermarriage. The general acceptance of racial differences in disease susceptibility spilled almost imperceptibly into an interest in studies of other traits less clearly "genetic." Success in explaining mechanisms behind a few genetic disorders lent credence to more general claims about mental capacity, gender, and socially desired or unwanted characteristics.

The 1990s began with enthusiasm for genetics, carried on the wings of startling progress in molecular biology. The very real power of new techniques to lay out detailed mechanistic causal chains for specific diseases commingled with studies that projected the medical model into the social realm. Historian of science Daniel Kevles pointed out how the genome project itself grew, in part, out of eugenics and might benefit from its lessons: "In its ongoing fascination with questions of behavior, human genetics will undoubtedly yield information that may be wrong, or socially volatile, or, if the history of eugenic science is any guide, both."[80] As the genome project gathered steam, its natural tendency to rhetorical overreach began to be counterbalanced by sympathetic

but critical colleagues in the humanities and social sciences. The ELSI research program would further feed this generally salutary development.

New genetic knowledge seems destined to bring genetic tests that will collide with a growing movement for disability rights. The battleground is likely to be prenatal genetic testing. For a disorder such as Tay-Sachs disease, an unremitting and severe disorder in which children are in essence born dying, prenatal testing is generally accepted. Abortion of a prospective child destined to a short life filled with pain and inability to respond to the world is, to most, a morally acceptable if tragic choice. Abortion for conditions with greater clinical variability, with a mix of genetic and environmental causes, of lesser severity, or with late onset are less obviously beneficial. To those for whom abortion is morally wrong, prenatal diagnosis followed by abortion will not be an option. Prenatal diagnosis may perhaps enable treatment before birth or soon after, or may yield information about what to expect. Theirs is the only moral scenario in which the responses to the new technologies are relatively clear—don't use them or use them only for information and treatment. To women for whom abortion is morally acceptable, the choices are more difficult to sort out. Aborting a fetus with a genetic disease is agonizing and painful, like the death of a wanted child. The new technologies create a more tentative pregnancy, in the words of sociologist Barbara Katz Rothman.[81; 82]

Choosing abortion on the basis of an expected disability raises the specter of choosing what kind of children there should be. The choices implicitly force judgments that echo debates about what lives are worth living, arguments that in an earlier era mushroomed into Nazi atrocities. To some in the newly vibrant disability rights movement, it is an ominous development. Someone born with a disability that is diagnosable before birth can point out that if the diagnostic technology had existed while they were in gestation they would not have been born. Their lives are patently and obviously worthwhile. How can preventing the births of others like them be right? This poses not only a practical, but also a deeply philosophical dilemma. University of Wisconsin philosophers Daniel Wikler and Eileen Palmer have noted:

> The charge that medical genetics is a potentially threatening eugenic program begins with the observation that much of medical genetics aims to combat disease not by healing anyone but by preventing the conception or birth of afflicted individuals . . . by picking and choosing among the potential people who might be conceived and born. . . . There are increasing signs, in the United States and Western Europe at least, that some disabled people increasingly identify themselves as a social group. . . . there is a strong disability rights movement, with political influence, there are leaders, and newsletters, and even radical and conservative factions. . . . Advocates of the disabled have urged, for example, that television programs show actors who seem ordinary in most ways but who may be blind or who utilize a wheelchair.
>
> For medical genetics, the disability rights movement is of particular importance. It

amounts to an ideological challenge, and it is mounted by the movement's most assertive, radical wing. The point of the radical disability rights critique is that even major disabilities, such as blindness, can under more just social conditions be merely one item in a very large inventory of life circumstances in which an individual might find himself; it is unfair to these people both to fail to create circumstances which minimize the burden of the disability and also to exaggerate the importance of the condition so much that it means that the person is thought of by others primarily in reference to the disability . . . Rather than prevent the birth of these kinds of people, they argue, we should change our attitudes about them, accepting them as equals and as essentially unremarkable.[83]

This is no mild conundrum. Adrienne Asch, a bioethicist long interested in disability questions, has taken a novel tack in considering abortion to avoid a child's future disability. She accepts a woman's *legal* right to choose to terminate any pregnancy, based on wanting or not wanting a child, and thus far remains in the feminist mainstream. But she parts company with many women in questioning the *moral* legitimacy of *selective* abortion for any but the most severely disabling conditions.[84;85] She accepts abortion to prevent the birth of children with disorders such as anencephaly or Tay-Sachs, but questions abortion of children destined to develop cystic fibrosis or Down's syndrome, for example. She leaves the legal door open to such abortions, but believes that women might be persuaded not to walk through it on moral grounds. It is a subtle argument aimed at women's consciences, not legal rules.

Another tack to address the hard choices about abortion, genetics, and new reproductive technologies is to focus on nurturance. Ruth Schwartz Cowan, a historian of technology at Stony Brook, poses the principle this way:

An embryo cannot become an infant unless it is nurtured; an infant cannot become an adult unless it is nurtured and—at the other end of the developmental spectrum—adults who are ill or disabled cannot continue to live unless they too are nurtured. Nurturance is a continuous, day-to-day, mundane process: feeding, sheltering, protecting, assisting. Its goal is, in the case of embryos, to create an individual who can have a relationship with other individuals, in the case of adults, to maintain and sustain the life of an individual who has relationships. . . .

If this principle were to be taken seriously it would follow that when individuals cannot, for whatever reasons, make decisions for themselves, the person or persons who have the right to make the decisions are those who are nurturing the individual. Whether or not we agree that a fetus is an individual we can still agree that it is not capable of making decisions about itself. This means that decisions about an embryo or a fetus which is *in utero* ought to be made by the person in whose uterus it is developing; this person may or may not be its biological mother or its intended social mother, but certainly won't be its father or a doctor, or the governor of the state in which it happens to be located.[86]

Philosophers Wikler and Palmer take another way out, drawing a distinction between choices about imagined future children as opposed to loving those children actually born, with or without disability. They argue:

> . . . A prospective parent is in a quite different context of moral choice than the parent of an actual child. . . . Before the child comes into being, we favor one list of attributes—the healthier ones—over another, if we get to make that choice. This is quite common. But it is unusual to find a parent who wishes that some other parent's child were his, even though each of us knows children in other families who are superior in some respect or other to our own. Thus before the fact we hope for a healthy child, but after the fact we do not regret having the children we do.[83]

They thus apply a concept from moral philosopher Thomas Nagel to the case at hand. Philosophers, social scientists, clinicians, scientists, and those making choices on this ethical frontier cannot help but confront questions for which the answers are but partial and tentative. The thorny and extremely divisive debate about abortion is certain to pervade future debates about biting into the fruits of genome research. Hovering behind the specific controversies about eugenics, disability, abortion, privacy, and other social, legal, and ethical issues is the social history of genetic explanation.

The dangers of genetic deterministic overreach are fed by claims about the power of genetics to explain what we most want to know. For those who toil each day in research laboratories in quest of disease genes, it seems a natural truth that finding genes and their products will illuminate function, and that would be a good thing. Indeed it is, but the public response to the advance of genetics is not received in this context.

Finding a link between Alzheimer's disease and a chromosome region for the Ross family, for example, would be an intriguing scientific clue. It is a long way from finding such a linkage to finding the gene, however, and it is already clear that there are several genes that might cause Alzheimer's disease in families. It is also clear that genes do not wholly determine the disease, as identical twins can differ in age of onset by a decade or more.[87] Environmental factors are at work. Even if all the "genes for" Alzheimer's disease were to be discovered, there is likely to be a long and highly branched causal network. And this for a relatively well-circumscribed biological phenomenon—a disease running in families as a Mendelian trait. How much more complex are other human characters likely to prove?

The explanatory choice between genetic determinism and environmental determinism is a false dichotomy. There are times when a powerful genetic prediction is possible. (Carrying the gene for Huntington's disease, for example, strongly predicts that the disease will ultimately appear. Even here, however there are large variations in severity and age of onset.) Most diseases lie far from this polar extreme, and general characters such as intelligence and athleticism farther still. The point is not that genes don't matter for such characters, or that science will never find "genes for" such characters, but rather that the relative power of the genetic explanation should not be projected from the case of Huntington's, where it is high, to the case of alcoholism or schizophrenia or, worse still, to criminal proclivity or intelligence.

Social analysts differ in their analysis of how dangerous and pervasive genetic determinism will prove to be. The history of eugenics and racial hygiene is enormously disturbing, but it occurred without the countervailing forces of critical scrutiny from inside or outside science and medicine. The genome project seems unlikely to escape such scrutiny, and indeed is nourishing it. Moreover, the Holocaust grew from a political environment fraught with problems much worse than biological determinism. Nazi racial hygiene was fueled by the biology of its day, but the biology did not cause it. As Daniel Kevles once observed, "if a Nazi-like eugenic program becomes a threatening reality, the country will have a good deal more to be worried about politically than just eugenics."[88] He added, even more cogently, that "if we do not use our knowledge wisely, it will be a failure not of science but of democracy."[89] The caution is apt, because we all know of many such failures.

Those who craft public policy, whether from executive offices or legislatures or kibitzing from the academic sidelines, might find little consoling about the fact that totalitarian eugenics would require political apocalypse. A milder but more sustained encroachment on liberties might prove pervasive without authoritarianism. Genetic discrimination and abuse of private genetic data are conceivable, and indeed likely, without policies devised to counteract them. The relative power of science and its critics is far from clear. Howard Kaye, a sociologist at Franklin and Marshall College, has observed:

> As our latest attempt at dropping some moral anchor, biology may prove as ambiguous and unsuccessful as previous scientific moralities—and perhaps even more harmful. Our current infatuation with biology, unlike that of a century ago, is occurring at a time when the humanities and social sciences have declared moral bankruptcy, thus depriving us of a vital part of the collective memory we need to regulate and resist our increased capacity for genetic manipulation.[90]

Kaye worries further that "the cumulative effect of the ways such knowledge is likely to be interpreted for and by the broader public will push us, like sleepwalkers, toward the biologizing of our lives in both thought and practice."[90] Genetics might indeed overshoot its actual accomplishments, inserting itself unobtrusively into the unquestioned premises of common culture. Or it might not. Kaye's caricature of 250 million people corralled passively by a thousand or so scientists seems no more accurate a portrait of the future debate, for its pessimism, than the optimistic visions of genome enthusiasts. The critics are also prone to rhetorical excess.

A future in which genetic determinism implodes scientifically as a consequence of its explanatory failures is equally plausible, just as Newtonian mechanics collapsed in the face of the probabilistic physics of quantum mechanics earlier in the century. This seems not merely possible, but likely. Both an expansion of genetic determinism and a weakening of its foundations seems likely to follow, affecting different people in different ways. While those confronting human genetic disease in clinics day by day are unlikely to fall prey to

simple genetic determinism, the culture is nonetheless vulnerable to muddle-headed claims about the genetics of intelligence and criminality.

A compact disk containing the DNA sequence of President Abraham Lincoln's genome would tell us very little about the President that we would really want to know. Whether or not he suffered from Marfan's syndrome, a genetic disorder not yet described in his time, would be a minor embellishment in his biography. It is of interest to historians of medicine and human genetics, and might have been of interest to Lincoln himself when choosing whether and how to have children, but the DNA sequence can contribute only a small increment to our understanding of his political ascent and the conduct of his presidency. Blanket generalizations about the worth and danger of genetic information, robbed of their specific social context, render them almost meaningless. And that was the whole point of the genome debate.

Watson's simple dictum to "just do good, and don't care if it doesn't seem good to others" gave way to a recognition that building the scientific foundations required public trust, and a major commitment to systematic exploration of how genetic science would work its way into the world. It was a complex process that would evolve with the science. In hearings for the 1993 NIH genome budget, Watson noted that the ELSI program's budget had risen from 3 percent to 5 percent in 1992, and further indicated, "I would not be surprised that five years from now this area will be 10 percent of our budget."[91] Trust in science involved a renegotiated social contract between scientists and the public that supported their work—those who would bear the brunt of any adverse impacts. The price of intellectual autonomy and support through public monies was continual public scrutiny of the scientific process and its results. The genome project placed genetics under that magnifying glass, where its past would be judged and its future assessed. The ELSI program was an attempt to make the negotiation process open and explicit. Attaching public bioethics to the scientific research program was a new anharmonic in the cacophonous din of democracy.

17

Bioethics in Government

A HEARING ON November 9, 1989, marked Senator Albert Gore's return to the issue of genetics. There had been several hearings in the Senate and House focused on the genome project, and most had touched on ethical issues, but the Senate Subcommittee on Science, Technology, and Space was the first to devote a hearing specifically to social implications of the genome project.[1] Among members of Congress, Gore had long associated himself with ethical issues in human genetics and reproductive technologies. While chairing a subcommittee in the House of Representatives during the early 1980s, he presided over a series of highly publicized hearings on human gene therapy, genetic testing in the workplace, and new reproductive technologies. In 1984, Gore ran successfully for the Senate. His interests in genetics continued unabated, but he was too junior in the Senate to have a platform on which to exhibit them, and a 1988 effort to be the Democrats' presidential nominee took him away from bioethics. His first opportunity to air those concerns came when he assumed the chairmanship of the Science, Space, and Technology Subcommittee of the Committee on Commerce, Science, and Transportation in 1989. Soon after assuming the chair, he scheduled a hearing on the human genome.

The highly public debate about the genome project and well-publicized successes in finding the cystic fibrosis gene and others had rekindled public interest in human genetics. The genome project would clearly result in much greater knowledge about human genes and would produce technologies to make genetic tests faster, cheaper, more accurate, and applicable to many more diseases. The issues of genetic discrimination in employment and insurance and the prospects of backdoor racism through genetic screening and testing became more urgent because of the genome project. Genetic testing and genetic discrimination had been topics of considerable public debate in the 1970s and early 1980s, sparked by genetic screening for sickle-cell disease and the recombinant DNA controversy, but the issues had lain dormant for several years.

In its 1983 report on genetic counseling, the President's Commission for

the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research presciently noted that the issues were unavoidable:

> Within the next decade screening for cystic fibrosis may be possible. This could be of great benefit. If adequate preparation for its introduction is not made, however, it could also create serious problems. . . . The possible demand for millions—or tens of millions—of tests in a short period of time, and the consequent need for follow-up diagnostic studies and counseling, is daunting in itself. The Commission . . . encourages continued attention to this area by government officials, as well as by people knowledgeable about relevant scientific, ethical, social, and legal concerns.[2]

The President's Commission's reports on gene therapy and genetic screening were aimed at reaching policy guidelines. The President's Commission built on earlier work on genetic testing and screening by the Hastings Center,[3,4] the National Academy of Sciences,[5] the March of Dimes,[6] and other groups. Soon after releasing its genetic screening report, however, the President's Commission passed out of existence. No federal body existed to monitor implementation of its recommendations.

Its successor, the Biomedical Ethics Advisory Committee and the congressional Biomedical Ethics Board, got stuck in the quagmire of abortion politics. These Siamese twins—a congressional board linked to an outside advisory committee and staff—grew out of a bill introduced by Senator Gore in 1983. Debate about a national commission on ethical and social implications of genome research has had a long history.

The idea for a federal bioethics commission grew out of the remarkable success of two previous bioethics commissions, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and its predecessor, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[7] When the National Commission was first created in 1973,[8] pundits forecast failure and endless controversy.[9–15] It was created over considerable opposition from scientists and clinical investigators wary of regulatory incursions into research. The Nobel Prize–winning biochemist Arthur Kornberg and the noted cardiac surgeon Christiaan Barnard testified before the Senate that a national commission would hand a license to pen-toting bioethicists who would hold up a healthy research enterprise.[16] When Senator Walter Mondale searched for a famous scientist to support his view that a commission was needed, he found only a few; the one he chose to quote in support was James Watson.

The fear of the day was that methods emerging from embryology would enable the cloning of humans. Watson spoke before a special meeting of the House Committee on Science and Astronautics and discussed recent developments in embryology and genetics. He warned that "any attempts now to stop such work using the argument that cloning represents a greater threat than a

disease like cancer is likely to be considered irresponsible by virtually anyone who understands the matter." Having defended the importance of free biomedical research, however, he went on to note the need for public discussion of its applications to humans, especially reproductive technologies:

> It is absolutely essential that within the United States, if not in every other country, very important committees be set up basically to know the state of the art . . . and inform the public as a whole. This is a decision not for scientists at all. It is a decision of the general public—do you want it or not? It is not a question for a group of scientists to decide . . . it is a decision which the people as a whole must make. . . . If we do not think about the matter now, the possibility of our having a free choice will one day suddenly be gone.[17]

Senator Mondale began movement toward a commission in 1968 and repeatedly introduced legislation to create one, but it failed in several Congresses for want of House support. In the early 1970s, concerns about heart transplantation and the onslaught of new and powerful genetic technologies intensified concern. The question of fetal tissue research emerged as a national issue. In April 1972, the *Washington Post* reported that NIH scientists were using aborted fetuses for research in Finland, provoking demonstrations and calls for a halt to such research.[18;19] A series of scandals further indicated to Congress that biomedical researchers could not keep their own house in order. Highly publicized Senate hearings between February and July 1973, before Senator Edward Kennedy, uncovered incontrovertible evidence of research abuse—Tuskeegee syphilis trials that left a cohort of four hundred poor black males untreated for decades; hepatitis experiments that inoculated young, mentally infirm residents of the Willowbrook facility with live virus; injection of cancer cells into senile patients at the Jewish Chronic Disease Hospital; use of prisoners to test drugs; whole-body-radiation experiments sponsored by the Department of Defense; testing of hormone analogues among welfare mothers and Mexican-American women.[16;19;20] These disclosures undermined those opposed to a commission, and a bill finally passed both houses. President Ford signed it into law on July 12, 1974.[19] The National Commission's first mandated task was to address one of the most contentious issues, fetal research, in a report due three months after it started work.[18] It seemed an impossible task, and well it might have proved to be. The National Commission, however, surprised almost everyone by producing reports with direct policy impact and lasting scholarly value.

The National Commission operated from 1974 to 1978. In its opening gambit on fetal tissue research, the commission was forced to deal immediately with an explosive issue, provoking strong passions, street demonstrations, and opposition from powerful religious groups. The commission cut its teeth on fetal tissue research and went on to produce another seven reports.[21–30] Far from failing, the National Commission became a model of rational policy-making.[19;31] National Commission reports laid the groundwork for regula-

tions to protect human research subjects.[32;33] The commission also articulated the principles guiding its approach in the Belmont Report, a landmark in the history of bioethics as a field.[26] The Belmont Report drew out the three principles—beneficence, justice, and respect for persons—that governed the deliberations of the National Commission in its dealings with various problems and that subsequently dominated bioethics scholarship for the next decade. The National Commission went a long way toward establishing that part of bioethics related to public policy. Rather than dying in disgrace, it begat the President's Commission.

In November 1978, Congress created the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. Its mandate was broader than the National Commission's, encompassing the protection of human subjects in research but also extending into the delivery of health care. It was to supplant the National Commission, which had expired four years earlier. An Ethics Advisory Board operated in the Department of Health, Education, and Welfare (HEW) during most of this period, but the board's function was mistakenly thought to overlap with the new President's Commission. HEW assented to Congress's diversion of the board's appropriations to support the operation of the new President's Commission, beginning in fiscal year 1980. The new commission had not only a more general mandate, but also elevated presidential status, whereas the National Commission had operated autonomously in HEW.

The President's Commission, created by Public Law 95-622 (1978), operated from 1980 to 1983, issuing eleven reports.[2;34–43] Two of these dealt with genetics. The 1983 report on genetic screening and genetic counseling was quoted above. At a hearing on human gene therapy in November 1982, Gore presided over the release of the other genetics report, *Splicing Life*. Gore's idea for an independent bioethics commission came directly from recommendations in that report. Alexander Capron, executive director of the President's Commission, was the star at this, the first congressional hearing I ever attended.[43;44] The proposal for an autonomous bioethics forum was transformed into a congressional body under pressure from Senate conservatives, particularly Jeremiah Denton.

Several Senators—Gordon Humphrey, William Armstrong, Jesse Helms, and James East—were particularly incensed at the President's Commission report *Deciding to Forego Life-Sustaining Treatment*,[39] which asserted that feeding and hydration were like other medical treatments and could thus be stopped in some cases. If there was to be a bioethics commission, these senators wanted it more cognizant of their views. This was the argument that brought the bioethics board under Congress's thumb, modeled on the Office of Technology Assessment. The newly reshaped bioethics forum emerged from a House-Senate conference over the NIH authorization bill in 1984. Anthony Robbins, staff physician for Rep. John Dingell, and David Sundwall, staff physician for Senator Hatch, were the principal architects. This new bioethics body was

incorporated into the Health Research Extension Act that was passed over President Reagan's veto in May 1985.[45]

Creation of the congressional Biomedical Ethics Board and Biomedical Ethics Advisory Committee (BEAC) ended the string of successful federal bioethics commissions at two. If the President's Commission and National Commission were home runs, the Biomedical Ethics Board was a strikeout. The board and the advisory committee operated effectively for less than a year, from September 1988 through September 1989, although they existed on paper and consumed considerable energy within Congress from 1985 through 1990. BEAC and the staff it was authorized to hire were responsible for conducting the work and producing reports. BEAC's members were screened and selected by the congressional board in a process that took over two and a half years. BEAC finally met in September 1988, four days before its initial authorization was to expire. Alexander Capron, who had been executive director of the President's Commission, was elected chairman; Edmund Pellegrino, one of the nation's best-known physicians in bioethics, became vice chairman. At the eleventh hour, Congress reauthorized BEAC and its congressional board for another two years. I was hired as acting executive director in December 1988.

The appointed committee members worked well together at both meetings the committee managed to hold before dissolving. A September 1988 meeting focused on election of a chair and vice chair and agreement on operating rules. A February 1989 meeting focused on human genetics. BEAC had a congressional mandate to report on ethical problems related to "human genetic engineering." The committee interpreted this to mean gene therapy as well as uses of genetic testing. Mandates for two other studies had later deadlines and shorter legislative histories, and were politically more complex, so they were moved to the back burner while the committee worked to establish a successful operating style.

LeRoy Walters testified before the committee, as chairman of the NIH subcommittee that oversaw gene therapy. Walters saw little need for yet another report on gene therapy, but much need for thought about uses of genetic testing and screening. He recounted the conclusions of seventeen reports from around the world, all of which agreed that somatic-cell therapy (affecting only the person treated) was morally equivalent to other kinds of therapy. Gene therapy that would cause inherited changes, by affecting sperm and egg cells or early embryos, lacked this consensus, but was technically difficult and unlikely to become practical in the foreseeable future.

Not only was there consensus on policy, but also Walter's committee at NIH as well as the Food and Drug Administration was actively engaged in overseeing the first gene therapy trials. Policy regarding gene therapy was thus thoroughly scrutinized. The same could not be said for uses of genetic tests, where there were many unresolved issues ripe for inquiry.[46] Neil Anthony Holtzman (Johns Hopkins), George Cahill (Howard Hughes Medical Insti-

tute), and Daniel Kevles (Caltech), the other invited speakers, concurred.

The committee decided to focus attention on issues of genetic testing and screening and the potential for discrimination in private insurance and in the workplace. The Biomedical Ethics Advisory Committee was poised to start this first project. It was on the verge of commissioning papers when its congressional board blew apart. Distrust among members of the board grew from 1985 through 1988 in the process of appointing BEAC members. The board fell into deadlock when liberal Republican senator Lowell Weicker lost his reelection bid and was replaced by Oklahoma conservative Don Nickles. The advisory committee might have lived on, but one member, the highly respected pro-life lawyer Dennis Horan, died. This left a troublesome vacancy. Gore promised the conservative Senate members that the slot would be filled by a pro-life candidate, but his staff person Gerry Mande tossed out the idea of several strong pro-choice candidates (among them Kate Michelman of the National Abortion Rights Action League and Faye Waddleton of Planned Parenthood) before learning of the deal his boss had made. The miscue proved more than the board could bear, and it broke in two.

A March 7, 1989, meeting of the Senate members devolved into a shouting match between Senators Gore and Humphrey, over the degree to which the pro-life and pro-choice power balance was assured on BEAC. They argued back and forth about who had promised what to whom. Tempers were already hot amid a partisan and acrimonious fight over John Tower's confirmation as Secretary of Defense (a nomination ultimately rejected by the Senate). After this meeting, BEAC was cut from its moorings and set adrift. As I heard the senators yelling at one another, I could vaguely sense my job disappearing and the nation's only national bioethics forum crumbling to dust. My first reaction was fascination that decisions could be made this way, not like my image from eighth-grade civics, with all those impersonal checks and balances of power. Stunned amazement soon collapsed into cynicism, which never entirely dissipated. The good-humored support of chairman Capron and fellow staff person Clair Pouncey were the only redeeming features of a long and frustrating period.

We labored mightily for months to find common ground that might save BEAC. Despite protracted negotiations, the board and the advisory committee died at the end of the fiscal year, and with them the main federal forum to discuss the issues of genetics and public policy. As it turned out, Senate conservatives Gordon Humphrey and Don Nickles killed the agency. If they had not done so, however, Rep. Henry Waxman, a liberal Democrat, was rumored to be waiting in the wings to do likewise. Distrust of the committee was intense from both ends of the political spectrum, with both believing they had conceded too much to their ideological opponents. Congress simply did not trust its own creation.

The power that flows through Washington is the cause of the syndrome known as Potomac fever. The power is real, but evanescent. I will long remem-

ber calling an appropriations committee staff member in the waning days of fiscal year 1989 to find out whether I should show up for work the following Monday. The appropriations bill, which was still pending, was no longer a set of abstract words that affected some distant federal agency, but the source of my paycheck four days hence. When the committee staff director did not pick up the thrust of my question, I asked bluntly: "Can I get paid next week?" He replied: "I hadn't thought about that. . . . I guess you're right, you can't." Nickles's staff crafted the language to kill BEAC and did the eleventh-hour maneuvering to insert it into the appropriations bill just days before the end of the fiscal year. They never called to warn me that I might be wise to look for a job. The demise of the BEAC, with a passing reference to my unemployment, was covered in the *New York Times* a few weeks later. Friends from all over the country called to ask what had happened. With a few days' notice, I was a thirty-five-year-old former executive director on the streets. Welcome to Washington.

Gore's November 9, 1989, hearings consolidated NIH's ELSI program and extended it into DOE. If Watson's notion was open to question before, it was thereafter locked in place by clear congressional intent. Watson saw where Gore would likely lead. Watson featured the ELSI program in his opening statement before the subcommittee. Robert Wood, acting director of DOE's Office of Health and Environmental Research (out of which came the genome program), spoke after Watson.

As Wood was reading his prepared statement, Gore pushed aside his microphone and turned to his staff. He asked if DOE had made a commitment of funds to match NIH's ELSI program. Gore then interrupted Wood to ask him directly. Wood began to answer that NIH would address the necessary ethical and legal issues, although DOE was quite concerned about them. Gore came back at him, asking specifically whether DOE had a budget commitment similar to NIH's. Gore suggested strongly that DOE have one. The senator warned of future hearings on the genome project where this would come up. Gore's position was endorsed by Senator John Kerry. It was as clear a signal as Congress could send.[1]

Despite this warning, at the December 1989 meeting of the joint NIH-DOE advisory committee, Ben Barnhart, director of the DOE genome effort, was not certain whether DOE would directly fund "ethics." Watson warned: "If you don't, Congress will chop your head off."[47] Charles Cantor, Robert Moyzis, and Anthony Carrano, all directors of the national laboratory programs supported by DOE, concurred with Watson and expressed genuine interest in joining the NIH ELSI program. Congressional pressure, the interest of Energy Secretary James Watkins, and support within the national laboratories brought DOE back to where DeLisi had left it several years earlier. DeLisi intended to fund bioethical analysis, and he met with LeRoy Walters at the Kennedy Institute of Ethics to discuss the possibility in 1987, long

before NIH evinced an interest. DeLisi left DOE, however, before an ethical and social analysis program was in place, and the trail disappeared for two years. Following discussion at the December 1989 meeting, DOE agreed to cosponsor Nancy Wexler's ELSI working group, making it a joint NIH-DOE advisory body.

If the point had not already been made, Congress's concern about social and legal issues was brought home where it really counted, in appropriation hearings. In NCHGR's first appropriations hearings as an autonomous NIH Center, Congressman Obey pointedly raised questions about how insurers and employers might use genetic information to discriminate unfairly against individuals.[48–51] The House appropriations report for the 1991 NIH budget stipulated that NIH come up with a systematic plan to deal with such ethical issues and to develop specific policy options to address those issues.[48] The NIH genome office was thus the first science office with a congressional mandate to mount not only a scientific research effort but also a parallel program to forestall its adverse impacts. With almost no dissent, the appropriations committee ratified Watson's precedent. It also went beyond it, however, and moved in the direction of reestablishing a federal capacity for analyzing bioethics and public policy.

Congressional concern about the implications of genome research reflected ambivalence among the general public. The potential for discrimination on the basis of one's genes emerged as a policy issue just as the genome project was gathering steam. The technical debate about the genome project within science no doubt fueled this movement, but public concern grew even more from successes in mapping specific disease genes.

The utility of the RFLP map was being proved by results. Yet every time a new disease gene was mapped, a potential diagnostic test was also created. New diagnostics informed medical decisions about risks of developing cancer or heart disease or Huntington's disease, but this medical information was also of potential interest to employers and private insurers, among others. Such third-party use of genetic patient data raised a host of difficult questions. The promise of medical benefit was inextricably tied to the prospect of social harm.

While members of Congress and the general public did not partake of the technical debate about the wisdom of the genome project as a scientific program, they could instinctively understand their stakes in its results. The project would unleash a flood of new information about human genetics. In an unjust society, genetic information could be harmful. In a world full of computers, intimate information could fly out of control, with only weak, incomplete, and outdated protections for confidentiality. Once debate about the genome project joined with concern about genetic testing, public reactions to the project were principally channeled through discussions of how increased genetic knowledge would change individual choices. Journalists and teachers used social issues as a hook to draw their readers and students into the science.

Genetic testing and confidentiality of genetic data became grist for the media mill. A 1989 *Time* cover feature on the genome project dedicated two of its five pages to its ethical and social impacts.[52] The Gannett Foundation sponsored a conference in November 1989 at which journalists from around the country listened to experts consider "The New Genetics and the Right to Privacy."[53] *Health* magazine's cover feature wondered about "Tinkering with the Secrets of Life."[54] *Consumer Reports* made concern about genetic screening and health insurance a cover feature in July 1990.[55] Social impact was a prominent theme in a "Mad Scientist" article about Watson in *The New Republic.*[56] Features ran in the Sunday "Outlook" section of the *Washington Post,*[57] *The New York Times Magazine,*[58] the *Wall Street Journal,*[59] and other papers.[60–64] Genes had the *geist* if readers had the *zeit.*

Journalists did not invent public concern, they conveyed it. Dorothy Nelkin and Laurence Tancredi warned of the social power of biological information, especially genetics, in their book *Dangerous Diagnostics.*[65] Radio commentator Paul Harvey expressed the popular distrust of scientific elites:

> Genetic engineers are well aware that their science is frightening to a lot of people. Mostly behind closed doors, they have been exploring evidence that human genes can be manipulated to make us taller, healthier, more or less intelligent and more or less likely to commit crimes. . . . Yet, secretive as the genetic researchers try to be, some of their findings are finding their way into the public media. . . . The new technology of genetic probes has led us to the cause of muscular dystrophy and promises to lead us to a cure. Cystic fibrosis and Huntington's disease will be the next targets for molecular geneticists. And Alzheimer's and certain cancers. And—behind those still closed doors—who knows what else?[66]

Within science, there were concerns that the social impact of genetics was larger than could be managed. Liebe Cavalieri of the Sloan-Kettering Cancer Research Center noted how the quantitative change wrought by new genetic technologies would cause qualitative changes in public perceptions, some of them quite worrisome.[67] One ecologist suggested that the public was so woefully ill-informed about genetics that "until a concerted education [effort] is made, even walking along the human chromosomes may be too fast a pace."[68] The group associated with the Council for Responsible Genetics sponsored a symposium on the human genome project at the January 1989 annual meeting of the American Association for the Advancement of Science,[69] where Ray White from the University of Utah was the beleaguered genome supporter in a sea of critics. The council later issued two position papers, one a well-crafted paper on genetic discrimination and the other an incoherent rhetorical blast against genetic determinism.[70; 71]

The interests of private employers and insurers collided with an intuition that people should not be subject to discrimination on the basis of their genes. Like race and gender, genes were well beyond personal control. The dilemma was most acute for private health insurance, although the same principles

applied to employment and to other forms of private insurance (such as life insurance, mortgage insurance, disability insurance, automobile insurance, and long-term care insurance).

Genetic discrimination began when physicians started to take family histories. Indeed, stories about insurance denial, among families with Huntington's disease, for example, were well known to genetic disease support groups. Few outside the field of medical genetics knew this, however, and the practice affected only a small fraction of the populace. The practice was also not universal; some insurers did it, but others did not. Moreover, most Americans got their health insurance through their employers, and group policies traditionally had few exclusions. As the 1980s gave way to the 1990s, however, employers became far more attuned to health care costs and insurers ever more concerned about financial risks.

People who knew they would develop a disease, or even those who knew they were far more likely to do so than others, could load up with insurance, throwing off the actuarial tables and saddling an insurer with extra payouts. This undermined the whole premise of insurance, as a mechanism to protect against *unpredictable* events. This was more than a theoretical concern, since private social security firms had gone bankrupt earlier in the century, leaving policyholders bereft of benefits despite years of payments.

The potential conflict between predictive genetic testing and private insurance had been noted many times before. The President's Commission's 1983 report on genetic testing and screening did not address insurance specifically, but it loomed in the background.[2] By the time OTA reviewed issues surrounding genetic testing in an appendix to its 1984 report *Human Gene Therapy,* private insurance was already becoming a more prominent policy issue. Stephen Eckman, a summer fellow at OTA from the Wharton School, called several private insurers and found that they would likely use genetic data to make premium and eligibility decisions if such data were available.[72] Just a few years later, Neil Anthony Holtzman focused his insightful book *Proceed with Caution* on issues surrounding genetic tests and found private insurance one of the most vexing issues.[73]

The rancorous debates about AIDS testing and drug testing during this period sensitized the genetics community to the public policy issues surrounding medical tests. In 1988 and 1989, several new books devoted sections to genetics and private insurance.[65;74;75] The rising costs of private health insurance gave employers a financial incentive not to hire those who would incur health care costs. This affected not only the prospective employees themselves, but also any dependents who would be covered under employment-based health plans. Legal scholar Mark Rothstein, from the University of Houston, noted: "The problem with employer-provided health insurance is not that it is employer-funded . . . [but that] employers are increasingly acting as health insurance underwriters. The growth of self-insurance has operated to magnify this problem."[74]

Insurers began to take notice. Robert Pokorski, medical director at Lincoln National Life Insurance, chaired a task force on genetic testing and had edited a "white paper" for the Council.[76] The papers in the collection pointed out the pros and cons of using genetic information, particularly genetic test results, but made no policy recommendations. The white paper was discussed at a CEO-level meeting of the American Council of Life Insurance (ACLI) in July 1989, where I was invited to present my perspective as acting director of BEAC. Ian Rolland of Lincoln National Life wondered aloud whether the industry shouldn't get behind legislation to level the playing field, proscribing insurance use of genetic tests. As it was, if one company used the tests, all companies might have to follow suit or risk losing a competitive edge. If genetic information was not used by any firm, however, then such competitive pressures would not build up. Those with genetic disease were, after all, already accounted for in actuarial tables. Rolland argued that the social contract between insurers and the public might demand that insurers refrain from assessing genetic risk factors. Most of the rest of the other CEOs were more skeptical about whether genetic factors could be factored out.

Within months, the insurance question had "arrived" as an issue. Pokorski and others from private life insurers were constantly on the road giving talks. The Health Insurance Association of America (HIAA) also formed a task force on genetic testing. Jude Payne, who staffed that group, was invited to defend her industry in public almost weekly. Eric Juengst commissioned Larry Gostin of Boston University and Nancy Kass of Johns Hopkins to prepare background papers on the legal issues for the ELSI working group.[77;78] At a September 1990 meeting where these papers were discussed, the ELSI working group formed an insurance task force cochaired by Tom Murray and Jonathan Beckwith. The purpose was to mediate a productive debate at the national level.

The insurance issue was further complicated by its regulatory framework.[74;75;79] Much of the analytical capacity for thinking through public policy resided at the national level, but the relevant statutory law and regulatory power resided in state governments. As the debate intensified over reform of the health care system, genetic illness posed a particularly difficult dilemma. It pitted the interests of those who carried genes they could not control against the fiscal realities of a social policy full of inherent contradictions. A public consensus that health insurance should be an entitlement collided with the reality that health insurance was allocated through a private market that could not be both fair and purely competitive.

HIAA and ACLI issued a joint policy statement in February 1992, companion to an ACLI report on confidentiality.[80;81] The HIAA-ACLI task force concluded that a more consistent rationale and set of principles would be desirable in dealing with the confidentiality and use of genetic tests.[80;81] The ACLI document, in particular, noted that "the point here is that in the newly

emerging area of genetic test information, adherence to principles rather than complex strictures may well be the preferable approach."[80] While aimed at avoiding an extremely complex and impenetrable regulatory framework, it was even more a call for just the sort of analysis at which the National Commission and President's Commission had excelled.

The critique from policy analysts and academics was overwhelmed for a time by a media blitz orchestrated by activist Jeremy Rifkin. On April 19, 1988, Rifkin held a press conference to propose a "Human Genome Policy Board" and "Human Genome Advisory Committee" modeled on the Biomedical Ethics Board and Advisory Committee.[82–85] The press conference was timed to precede an April 27 hearing before House Energy and Commerce chairman John Dingell, at which OTA's genome report would be released. Rifkin's list of supporters included Judith Areen (dean of the Georgetown Law School), Robert Murray (Howard University), Patricia King (Georgetown Law School), public activist Ralph Nader, Marc Lappe (University of Illinois), and James Bowman (University of Chicago). They were all genuinely concerned about genetic discrimination. Rifkin parlayed their interest into support for his initiative and used their names to lend prestige to his insatiable quest for publicity.

Rifkin next linked the genome project to a suit seeking to block the first human gene transfer experiment. On January 30, 1989, he brought a coterie of disability rights activists to a meeting of the Recombinant DNA Advisory Committee (RAC), which was in the process of reviewing the clinical protocol. He announced his lawsuit and opposition to the genome project until NIH set up an "Advisory Committee on Human Eugenics."[86] The composition of Rifkin's proposed committee bore an uncanny resemblance to his Human Genome Advisory Committee of the year before, despite its different purpose. The RAC "respectfully declined" his suggestion, while agreeing that workplace discrimination and insurance discrimination were issues that needed attention.[87] RAC saw no reason to couple these issues to gene transfer and cancer treatment.

Rifkin linked legitimate policy concerns, assembled an *ad hoc* coalition of distinguished supporters, targeted the salient genetics topic of the day, fanned public fears of eugenics, and kept himself at the center of attention. The press release quoted Rifkin as saying that "if we are not careful, we will find ourselves in a world where the disabled, minorities, and workers will be genetically engineered."[88] Being careful might well mean locking the door and throwing out the key.

According to Rifkin, blocking the threat of genetic discrimination justified stopping an experiment to mark cancer-killing cells in patients with terminal malignant melanoma. Hindering improvements to treat one disability (cancer) was his policy response to speculative dangers that might someday materialize

if we slid down a slippery slope toward genetic treatments for other disabilities. A cynic might be forgiven for thinking this was a publicity stunt more than a bona fide attempt to improve public policy.

A copy of the lawsuit to block the experiment was passed out at the RAC meeting, but it was not filed for several weeks. NIH subsequently settled out of court, under terms that were not made public. Rifkin claimed victory, and NIH went on to approve the gene transfer protocol.

In the genome press conference and the suit against gene transfer, Rifkin was repeating earlier forays into the public discussion of genetics. Rifkin was a former class president, cheerleader, and economics major from the University of Pennsylvania who cut his political teeth in the antiwar movement of the late 1960s. He shifted his attention to biotechnology in the 1970s, drawn by the recombinant DNA controversy.[89] In 1977, he published a book with Ted Howard, *Who Should Play God?*[90] Rifkin followed this in 1983 with *Algeny,* a book against gene therapy.[91] Soon after *Algeny* was published, he organized a coalition of prominent clerics to oppose gene therapy of the germ line, which would produce inherited changes, not only in the persons treated but in some fraction of their progeny. (Germ line therapy could ensue from genetic alterations of sperm, eggs, their precursors, and cells of an early embryo.) Rifkin sent a proposed resolution to his coalition members. He then forwarded the resolution to Congress, along with a "Theological Letter Concerning the Moral Arguments Against Genetic Engineering of the Human Germline Cells."[92;93]

Senator Mark Hatfield introduced the resolution in the Senate, where it died.[94] The "Theological Letter" was adapted from sections of Rifkin's book and argued that once any form of gene therapy began, society would be unable to stop it. Gene therapy for a serious genetic disease today, genetic enhancement of intelligence and athletic ability tomorrow.

It turned out that the signatories to the resolution had not seen the "Theological Letter" that accompanied it, and many later recanted their support.[95–98] A group of clerics met in August to declare that the June 8 resolution had been "unnecessary and misleading."[99] They continued to be concerned about germline interventions, but no scientist was actively proposing them. Some of the clerics surmised they had been duped into promoting sales of Rifkin's book.

In July 1990, Rifkin met Watson briefly at the ABC studios in downtown Washington. They discussed how genetic information needed to remain confidential. Rifkin was proposing legislation to safeguard genetic information in the hands of the federal government. On July 24, Rifkin faxed a letter to Watson indicating that "John Fletcher, Tom Murray, Marc Lappe, William French Anderson, and others have all given their input on the bill." He warned that "many congressmen and senators on the Hill have expressed concern about continued funding of the Human Genome Project, worrying that the appropriate genetic privacy legislation needs to be passed 'before' the human

genome database and screening information are too far along. . . . Getting this bill passed by next spring may well be key to securing Congressional and public support of the Human Genome Project," hinting that support for the genome project might be bought by support of his privacy legislation.[100] Rifkin's five-page draft bill was translated by congressional staff into H. R. 5612, a twenty-five-page bill introduced by Rep. John Conyers on September 13, 1990.

This bill was a hard issue for Nancy Wexler's ELSI working group to handle. At the January 1991 meeting, Madison Powers of the Kennedy Institute of Ethics spoke about the weak legal protections for confidentiality. Even in medical settings, there were few laws to protect confidentiality, and they had many gaps. The notion of patient autonomy might well be projected from person to information, asserting "informational self-determination" to protect one's interests—including who had access to genetic information—as well as one's body. ELSI group members discussed the Rifkin and Conyers bills and agreed that further legal analysis was necessary. Lori Andrews of the American Bar Foundation agreed to look into mechanisms for developing confidentiality statutes that would more adequately address the major problems than did the Rifkin bill.

Rifkin's contribution was to highlight the weak points of genetics and biotechnology and to focus public attention on them. His flaws were a neglect of homework and poor grasp of policy solutions. He used lawsuits to block government action with some success, but policy changes that required sustained commitment, such as policy analysis and legislation, were generally beyond him. Indeed, he could be something of a liability to his allies. Those who worked with him were often tarred by the association. If Rifkin had taken a position, opponents had a ready-made rhetorical tool. They need merely mention his position to cast doubt on its wisdom.

Policy debate about the confidentiality of genetic information came out from under Rifkin's shadow in 1991. On April 24, 1991, the Conyers bill was reintroduced as H. R. 2045, stripped of its enforcement provisions. The accompanying press release quoted Conyers, who borrowed several phrases from the Nelkin and Tancredi book:

> The right to privacy is a personal and basic right protected by the Constitution. That right is now potentially threatened by major and important advances in the biological sciences that are expanding our understanding of the genetic components of human diseases. . . . Because of high-tech developments in gene mapping and screening, genetic privacy could become a major focus of the civil rights movement in the next twenty years. Allowing genetic information outside an individual's personal use threatens to open a "Pandora's box": we may well see genetic information used by the government and the private sector to create a "biological underclass" of those with "inferior" genetic makeups. One's genetic information should never be allowed to be used as a weapon against them.[101]

Sherille Ismail, Conyers's principal staff person for the bill, was initially optimistic about passage, but began to receive feedback from many quarters

about its weaknesses. Those who should be friendly to it were finding defects. The intention for the bill changed from seeking passage to using it as a vehicle to provoke discussion about what should be done.[102]

A well-publicized policy problem in France highlighted the complexities faced by privacy laws. A team of researchers culling through family records in Brittany inadvertently discovered a form of glaucoma inherited in some families.[103] (Glaucoma is a treatable eye disease, often detected only after there has already been irreversible damage to vision.) The French team constructed enormous pedigrees and could identify many at risk of going blind. French privacy laws prohibited directly contacting those at risk, however, and the National Commission on Informatics and Liberties (a national privacy commission) decreed that it would also be unwise to list specific individuals when notifying local physicians. Instead, the policy became one of informing physicians in the area to be on the lookout for glaucoma cases, as some families were at increased risk. In the United States, the decision would likely have focused on the individuals' ability to secure information relevant to their own health. The investigators might indeed have been compelled to find those at risk, but in France as in much of Europe, privacy weighed much more heavily.

The investigators had initially approached the privacy commission with a proposal to study several untreatable diseases, including the psychiatric condition manic-depressive disorder as well as glaucoma. The privacy commission was concerned about confidentiality and the possibility of stigma. It was also concerned about intrusions on the privacy of individuals if they were contacted directly by investigators they hardly knew. The privacy commission asked the investigators to drop the work on manic-depressive disorder and to work only through local physicians.[104]

The conflict between individual privacy and public-health case-finding, starkly shown with glaucoma in Brittany, also arose in genetic studies of breast cancer, colon cancer, cholesterol metabolism, and other treatable (or preventable) diseases. It was especially vexing for those studying p53, a protein associated with some cancers. Some families inherited a p53 mutation that made them far more likely to develop cancer. How to study such families, what to tell prospective participants, and how to handle complex familial dynamics were already difficult problems in such families, and became all the more so when children were involved. And yet 20 percent of children with the p53 mutation might die of cancer before reaching the age of majority, when they could make their own choices.[105]

Those studying large pedigrees afflicted with illness confronted the issues every day, but with little policy guidance. Information in such pedigrees was not as simple as other medical information. Genetic data about one member of a family also related to others in the pedigree. Knowing the genetic composition or the clinical status of one family member might well inform others about their risk. When the disease could be treated or prevented, the stakes were especially high. The need for coherent policies based on more than *ad hoc*

consideration began to become clear as geneticists discovered more genes predisposing to illness. The question was how to fill the policy gap.

The debate about social impacts was at least as active in Europe and Canada as in the United States, and was emerging in Asia as well. In Germany and German-speaking nations especially, human genetics labored in the shadow of eugenics and "racial hygiene." A spate of books emerged in the late 1980s, detailing how scientists and physicians promoted a racist agenda in the first half of this century.[106–112] The medical model of nondirective genetic counseling became dominant throughout the world in the postwar period,[113] and human genetics as a science explicitly rejected the tenets of eugenics and racial hygiene,[114] but the historical burden could not so easily be removed. Nonscientists were not going to give their trust automatically; scientists would have to earn it.

The Economic Summit nations (the so-called G7 nations) were joined by the European Commission at a meeting in Rome in April 1988 to discuss ethical issues surrounding genome research.[115] Bartha Knoppers from the University of Montreal noted that a new social contract was under negotiation. Individual genetic differences had to be accounted for in legal notions of equality.[116] Knoppers argued for a robust protection of legal equality despite genetic diversity. The connections between a person's genes and notions of human dignity, although murky, were clearly important to conceptions of the individual.[117]

Another contract was also being renegotiated between science and society. Science increasingly carried the mantle of responsibility for how the knowledge it produced was used. The genome project had taken a bold step by folding analysis of the social implications of genome research into the research plan itself. The notion of supporting a social analysis program along with genome research caught hold simultaneously in the United States, Canada, Europe, and Japan.

European efforts built on growing interest in bioethics and public policy. A series of reports stood as landmarks in the evolving debate.[118–129] The most public debate centered on the human genome component of the European Commission (EC) genome program.

The EC successfully launched genome research programs on nonhuman organisms in 1988. Plans were underway for a human genome program as well, but complex European politics came into the picture. Peter Pearson from the University of Leiden chaired a committee charged with formulating plans, until he moved to Johns Hopkins University, whereupon Malcolm Ferguson-Smith from the University of Cambridge took over. The scientific advisers recommended a three-year scientific program funded at 17 million ECU (European Currency Units, around $1.40 at the time). The European Commission plan was routed to the European Parliament. In the Parliament's Energy, Research, and Technology Committee, the bill was assigned to a reader, Be-

nedikt Härlin, a German Grün (Green Party member). The bill had a rough ride through the European Parliament.[130]

When the bill got back to the European Commission, the players had changed. Research commissioner Filip Maria Pandolfi now had authority. He was sensitive about uses of genetic information and held up the proposal for a time.[114] The proposal's name changed from "Predictive Medicine" to "Human Genome Analysis" in its parliamentary transit,[131;132] signaling a recognition of social concerns.

In 1988, the EC scientific advisory group formed a study group on ethical, social, and legal aspects (ESLA) of the Human Genome Analysis Working Party. Martinus F. Niermeijer of Erasmus University in the Netherlands chaired the ESLA study group, which prepared a series of documents and planned several public conferences and a program of activities to focus on implications of genome research. Inclusion of a program to consider the ethical, social, and legal aspects of genome research with a 1-million-ECU budget (7 percent of the total program budget) cleared the way for approval of the overall program.[133] It was approved by the council on June 29, 1990, with the proviso that the program would implement confidentiality protections and would explicitly exclude germ-line genetic manipulations.[134] In November, the EC genome program gave out its first batch of eighteen one-year grants from among forty-two submissions.[135;136]

In Japan, ethical analysis was also incorporated into the Monbusho (Ministry of Education, Science, and Culture) program, headed by Norio Fujiki, a medical geneticist from Fukui Medical School. A 1992 report from the privacy commissioner of Canada, *Genetic Testing and Privacy,* touched on medical testing, how insurers and employers might use genetic tests, and DNA forensics.[137] The Canadian genome program announced in 1992 also included a minimum 7.5 percent of its budget earmarked for analysis of social, ethical, and legal issues.[138] The development of bioethics studies in parallel to genome research was becoming an international phenomenon, but it was given the most resources in the United States.

Many months after its appropriations authority died, the Biomedical Ethics Advisory Committee reared its head again briefly, but only because of the ELSI working group. During 1989, the Americans with Disabilities Act was under debate in the House and Senate. Senator Tom Harkin and Representative Steny Hoyer introduced this sweeping revision of federal disability law, the first in well over a decade, into their respective chambers. Robert Silverstein, Harkin's staff director handling the bill, met with me briefly outside his office just before the Labor Day recess in 1989. We discussed whether the bill covered genetic disabilities and genetic testing. I also spoke with Chai Feldblum, an American Civil Liberties Union lawyer involved in drafting the bill. She noted that genetic disease had not been a major issue in deliberations about the bill, but the scope of its definition should encompass those with genetic disease.

The Americans with Disabilities Act was mentioned in passing at the Gore hearings on November 9, 1989,[1] and again at a Williamsburg, Virginia, ELSI meeting in February 1990, when Adrienne Asch pointed out its relevance to protection from genetic discrimination by employers. At that point, I dusted off some background memos from BEAC, written a year before.

As the bill neared final passage, I belatedly struck upon the idea of having the Biomedical Ethics Advisory Committee act, in its assigned role as adviser to Congress. The committee could not expend federal dollars, but it still existed on the books and retained its original mandate. The members had never resigned, nor had I done so as acting executive director. (They just stopped paying me.) BEAC's chair, vice chair, and acting director—Alexander Capron, Edmund Pellegrino, and I—sent a letter to Senator Harkin and Rep. Hoyer seeking clarification about whether the ADA covered genetic testing.

By the time we acted, the bill had passed both houses, but was held in a conference committee to resolve differences between the House and Senate bills.[139] The Biomedical Ethics Advisory Committee sent copies of its letter to congressional staff and outside groups working on the bill. The Council for Responsible Genetics sent a well-argued position paper along with collected cases of alleged genetic discrimination to Rep. Hoyer and Senator Harkin just a few days later.[71; 140] Congressmen Owens, Edwards, and Waxman noted how the ADA should prevent genetic discrimination in endorsement statements for the House, and Orrin Hatch did so in the Senate.[141; 142] Rep. Hoyer sent a letter in reply to the BEAC letter, indicating that genetic testing was never considered explicitly during debate, but the language of the statute was broad enough that courts would likely cover the situations of potential concern. Hoyer noted that implementation and interpretation of the statute would need to be monitored closely.[143] How right he was.

Mark Rothstein was an attorney at the University of Houston Law Center. His book on medical testing and the cost of employee health benefits included a section on genetic testing and insurance.[74] Rothstein followed the Americans with Disabilities Act closely. He urged the office implementing the statute, the Equal Employment Opportunity Commission in the Department of Labor, to interpret the statute so as to protect against genetic discrimination,[144] and he discussed his recommendations at a meeting of the ELSI working group in January 1991. Rothstein argued the Act should cover those expected to become disabled and also parents who were carriers of disease-associated genes. Employers might have incentives to discriminate against those who had a child with genetic disease, or were at risk of having one, because of expenses incurred under employee family health benefits.

If a prospective employee was a CF carrier married to another carrier, for example, employers might choose not to hire him or her, fearing the costs of medical care for a child born with CF. Rothstein argued that such discrimination should be proscribed, and was certainly within the intent of the ADA.

In draft regulations issued by the EEOC on February 28, 1991, genetic

testing was not mentioned, but a category of "conditional offeree" was created.[145] This was a person who had been tentatively offered employment, but was then subject to a broad range of tests and medical inquiries by the employer. By this stroke, the EEOC undermined the ADA. Rothstein was appalled by several interpretations of the statute embodied in the regulations.[146] He was invited to address the ELSI working group again at its April 1991 meeting in Los Alamos.

The first day of the meeting was the last day of the comment period on the draft EEOC regulations. Rothstein presented his opinion, and after some confusion about the group's authority to comment on draft regulations from another part of the federal bureaucracy, the ELSI working group quickly prepared a statement and faxed it to Washington just minutes before the comment period closed. The group urged EEOC to explicitly protect those carrying deleterious genes, but not themselves affected by them, from genetic discrimination. The statement also asked that the regulations reject the subterfuge of conditional employment offers, or at least narrow the range of what information could be gathered about job applicants.[147] Those tested should be told the results of their tests, and EEOC should erect safeguards to protect the confidentiality of medical information gathered about job applicants. The working group also encouraged good data-management practices to restrict access to only those who processed employee health claims, so that only those with a need to see personal data had access to them.[148; 149]

Nancy Wexler presented the ELSI working group statement to the NIH / DOE joint subcommittee on the human genome on June 15, and it unanimously endorsed the statement. Paul Berg and Sheldon Wolff, subcommittee cochairs, sent a letter to EEOC chairman Evan Kemp that summarized the central points.[150] These efforts had no impact on the final regulations, which were promulgated on July 26, 1991.[151] There was a significant irony, in that Evan Kemp had previously made strong statements about the dangers of genetic discrimination in another context.

Kemp supported Rifkin's proposed bill in 1989, soon after he took the reins of the EEOC from Clarence Thomas as the equal employment opportunity commissioner. (This office achieved national notoriety when Thomas was nominated to the Supreme Court in 1991 and allegations of Thomas's sexual harrassment of Anita Hill at EEOC became a national news sensation.) In 1989, Kemp noted that "the terror and risk that genetic engineering holds for those of us with disabilities are well grounded in recent events. Baby Doe was not an isolated case. Our society seems to have an aversion to those who are physically and mentally different. Genetic engineering could lead to the elimination of the rich diversity in our peoples. It is a real and frightening threat."[86] Two years later, Kemp's EEOC chose to interpret the Americans with Disabilities Act differently from the lawyers who wrote it, thus missing an opportunity to prevent genetic discrimination of a different kind.

The ADA experience was important because it indicated limitations in the

ELSI working group's ability to analyze and formulate policy. The working group was operating in a mode of short statements separated by three- or four-month intervals of inaction. A policy analysis group would have met far more often, and would have much more actively monitored political events and relevant developments in academia. Most important, the short working-group statements said what to do, but did not lay out the reasons why. The statements were prepared in haste and lacked the coherence borne of sustained deliberation and systematic data-gathering. Much of the value of previous federal bioethics commissions came from the documentation of reasons, which in turn came out of a complex feedback loop including discussions, solicitation of new information and commissioned papers, and further analysis. Repeated meetings of the commissions had characterized previous bioethics commissions, in the United States and abroad. A capacity to do policy analysis depended on several full-time staff and an active committee.

Beyond these process limitations, and arguably more important, the working group was buried several layers down in the NIH and DOE bureaucracies. It was advisory to a joint NIH-DOE subcommittee, in turn advisory to the main outside advisory bodies to NIH and DOE. The ELSI working group was advisory to an advisory group to an advisory group to two different government departments. If a recommendation got to the parent organizations, it might still have to transit several more layers en route to the outside world. NIH and DOE officers had not hindered the working group's freedom to make statements, nor was there any indication they would do so in the future. But if a working-group statement touched on policies of either parent agency, recommendations might well require review through the Department of Health and Human Services and through DOE's hierarchy. It seemed likely that at some time, the working group would encounter an issue that touched directly on sensitive policy matters, such as abortion. The group's hard-earned freedom might then disappear. The working group lacked a clear mandate from its executive sponsors or Congress. It also lacked official standing, such as a congressional warrant, to comment on the policies of other agencies.

The working group had directly promoted a new NIH policy on CF pilot testing, a research program within the purview of one of its two parent agencies. In research policy, it might thus exercise influence, but when it came to the first area of social policy, the result was less impressive. The EEOC had safely ignored the working group's comments on ADA. EEOC did not have to respond to the working group more than to any other member of the public. The lack of clout was not due to the competence or intentions of NIH or DOE officials. It was an intrinsic structural problem. While ample staffing and institutional support might increase the working group's stature, nothing could substitute for a congressional charge.

The experience also brought to mind another recent failure in public bioethics—the 1988 Fetal Tissue Transplantation Research Panel.[152–155] This panel was convened by the NIH director's office in September, October, and

December 1988 to deliberate on whether NIH should fund research to transplant fetal tissue. Preliminary experiments using fetal brain cells to treat Parkinson's disease and pancreatic cells to treat diabetes had been done abroad, and to a limited extent in the United States with private funds. A 1987 University of Wisconsin grant proposed to use federal funds for pancreatic cell transplantation. A survey of federal grants uncovered more than one hundred that employed fetal tissue over the decades, but NIH director Wyngaarden judged that the contemplated experiments that would employ fetal cells in transplantation would attract more notice and were likely to be controversial. He sought approval from his boss, the assistant secretary for health and director of the Public Health Service, then Robert Windom.

Windom reacted by imposing a moratorium on such research and requested that NIH convene a panel to scrutinize how use of fetal tissue in transplantation might relate to abortion—specifically whether it might encourage women to seek abortions. His staff drafted ten questions for the NIH panel to address, the first few of which focused on whether and to what degree tissue donation from a fetus might constitute an inducement to abortion.

As it turned out, the policy rationale turned on question 2: "Does the use of the fetal tissue in research encourage women to have an abortion they might otherwise not undertake?" This was a poor question to ask a group of "experts," as it was obviously an empirical one, subject to assessment by sophisticated survey methods, but the method chosen was deliberative. The question could only be answered by data, but no data were gathered, and committee discussion was sought as a substitute. In the end, the panel voted on a series of answers to Windom's questions. A report was filed, with three statements concurring with the majority positions, two dissenting statements, and a letter that was passably close to a dissent. The panel's report was considered by the NIH Director's Advisory Committee, which approved the majority position.[156]

Windom had imposed the moratorium in hopes of forestalling a more permanent restriction from the White House. He intended to lift the moratorium when "lo and behold, the hand from above denied me that privilege."[157] He later explained: "I thought at the time that by getting the interested parties to analyze the complexities of the issue before approval for the first implant would solve the problem once and for all; then we could go full speed ahead without hindrance. I also felt that if I did approve the initial request the White House would have overruled, and there might not have been the proper scrutiny of the issue, such that approval might never come."[158]

The process that started under Secretary Otis Bowen and Robert Windom in 1988 was then passed to Secretary Louis Sullivan and Public Health Service director James Mason in the new Bush administration. The new guard in the department was faced with a tough decision. In his Senate confirmation hearings, Secretary Sullivan had been given a rough ride over the abortion question by Senator Bill Armstrong, a strong pro-life advocate. Faced with the majority

recommendation from the NIH panel, Mason and Sullivan demurred, and extended the research moratorium indefinitely.

The deliberations of the panel had in essence been considered, but subordinated to political judgments that could have been made without benefit of such a panel. Part of the flaw was the topic at hand. Part of the problem was time, but the NIH panel took almost as long as the National Commission in its first report, but with remarkably different policy impact. The National Commission's report was almost directly implemented, and its report had a long shelf life, while the Fetal Tissue Transplantation Research Panel produced a series of reports with a confusing set of conflicting views. Another element was the rising role of interest group politics, and the significance of this cannot be fully judged, but is certainly significant. But of most relevance to the dilemma facing the ELSI working group—how to formulate policy options from a position within NIH—the process was also flawed.

In contrast to the National Commission, the Fetal Tissue Transplantation Research Panel was starved of staff and other resources. The first National Commission report lists sixteen staff, most of whom had direct training in law, ethics, or some field of substantive relevance to the commission's mandate. Many were well-recognized national experts. The 1988 report from NIH lists the panel members, but no staff. Several staff in the NIH director's office and a couple in the Office of the Assistant Secretary for Health were indeed focused on the fetal tissue effort, but they also had other duties, and bioethics was but a part of their job descriptions. A few outside papers were commissioned for the 1988 panel, most notably a legal background paper prepared by the Poynter Center of the University of Illinois, and many additional documents were contributed to it for consideration. This was a far cry, however, from the spate of reports prepared at the request of the National Commission. One important difference is that the National Commission sought papers after its meetings to decide what it needed to know. The NIH background papers were requested as preparation for the first meeting, and no further papers were ever sought after the panel actually met.

The 1988 panel had been expected initially to achieve consensus in a single meeting, perhaps by analogy to the format of NIH consensus development conferences. Such conferences were, however, most successful when convened around technical questions rich with data that were ripe for expert analysis. No bioethics commission operated in this manner, and for good reason.

It quickly became apparent that a second meeting of the fetal tissue transplantation panel was necessary. The expectation of a single meeting precluded systematic planning about what data to gather and which topics might warrant examination by hired consultants. Since the panel did not expect to meet again, there was no preparation of an agenda to find out what facts should be gathered, what views solicited. If at least two or three meetings had been anticipated at the outset, the first meeting might have been spent deciding what questions to address and how best to take advantage of outside experts, taking

pressure off the initial meeting and also deferring discussion of recommendations until the group had begun to work together. When the second meeting in October adjourned in near-chaos, a third meeting was scheduled for December.

Bureaucratic autonomy was just as important as the expectation of an extended series of meetings. Previous bioethics commissions had been given a mandate to report independently to Congress and the executive branch. They were handed topics, but not told how to address them. Much of the creative hurly-burly of policy analysis came from finding new approaches to old problems. In contrast, the 1988 panel was given a fixed list of ten questions to address, fixing the deliberations in a tight frame and precluding the best hope of creative consensus formation. Not only was the agenda set from above, but also the unrealistic schedule. Previous bioethics commissions depended critically on time to gather facts, to prepare background papers, and to discuss options among the commissioners. All these elements were rendered impossible by the framing of the questions and the expectation of immediate resolution.

Beyond these process flaws, and in part because of them, the product of the deliberations was ill suited to achieve its given ends. As one commentary in an Institute of Medicine report noted:

> Did [the Department of] Health and Human Services, and the public generally, get what it most needed from the panel's report? I would argue that it did not. What was most needed was not only a cogent, clarifying discussion of the issues by nonmedical experts but also a rhetorically and aesthetically attractive report. When one enters the field of public policy debate on issues that are as strongly controversial as abortion, one must find a language and a set of images that will help a polarized community begin to build a consensus. . . . What was lacking was a document of the style that is needed today: an eloquent, appealing, quotable report that can assist the decision maker both in making and later in defense of difficult policy decisions.[159]

Patricia King, who served on the NIH panel as well as the Institute of Medicine committee that reviewed its process, wrote another commentary:

> The drive to achieve consensus was central to the panel's work, and, indeed, consensus was achieved. Yet I believe that ultimately the product is not particularly persuasive. The fact that the panel's recommendations were not adopted by the Department is not the test of their persuasiveness . . . it failed to make clear how persons holding radically different views about abortion could nonetheless agree that the use of fetal tissue from induced abortion is "acceptable public policy" under specified conditions. It was probably necessary to *describe the process that resulted in acceptance* of this point rather than merely stating it [italics added].[160]

Some argued that the process had produced just what department officials wanted, a delay into the next administration and a confusing policy document. It produced a document that could be used initially to delay removing the research moratorium, and then because of its internal inconsistencies could be safely ignored, leaving the moratorium in place indefinitely. In conversations with staff and panel members involved, however, there was little evidence for

this cynical view. Rather the failure seemed more one of topic, process, staff, and timing than deliberate subterfuge. In bureaucratic terms, the lesson seemed to be that grappling with policy questions would require more time, more meetings, more staff, more commissioned papers, and more institutional autonomy.

The House Subcommittee on Government Information, Justice, and Agriculture explored the ELSI working group's policy analysis capacity in a hearing on October 17, 1991.[161] Rep. Bob Wise chaired the subcommittee, and the hearing was largely organized by subcommittee counsel Robert Gellman. The subcommittee had an abiding interest in issues related to privacy and data-management practices, tracing back to before the Privacy Act of 1974. The subcommittee had convened an earlier hearing on general privacy matters, including access to computer records, on April 10. The October hearing was focused on the genome program, and specifically the ELSI working group and the ELSI grants programs in NIH and DOE.

The subcommittee heard testimony from NIH director Healy, NIH genome center director Watson, Nancy Wexler, and David Galas, director of the life sciences research section of DOE. Jeremy Rifkin was there to promote his privacy bill, which had initially been a focus of the hearing, but had since been recognized as wanting by committee members and staff. Rep. Wise asked several questions about the ELSI grants program and ELSI working group procedures, the main theme of which focused on whether the welter of grants and contracts would congeal into useful policy options for legislators and executive branch officials. He was clearly skeptical that the ELSI working group could operate autonomously where it was currently situated. Healy detailed how a policy proposal would go from the genome office to NIH to the Health Department through OMB to the White House. Wise pressed Healy and Watson about how policy recommendations would rise out of a program of research grants, however competently carried out and administered by NIH and DOE. The gist of the replies was that it was too soon to tell. Healy complimented OTA on its capacity for policy analysis, but questions about policy analysis by the ELSI working group were left largely unanswered. Wise later came back to questions of structure. Healy then noted her experience on the fetal tissues transplantation research panel:

> NIH handled it in, I think, a very responsible way by bringing together groups that represented all parties and came up with a series of very well-thought-out policy recommendations. . . . the debate was elevated to the highest level. . . . it certainly is something that was not hidden in some back closet.[161]

Rep. Wise then asked if any witnesses cared to comment on whether genome research might not provoke passions surrounding abortion, because of the link to prenatal genetic testing. Healy replied:

> We do not believe for a minute that the human genome project relates to the issue of abortion. And abortion is also not an NIH issue. In fact, I will tell you, Mr. Chairman,

that one of the difficulties that NIH has faced historically is that people believe abortion is an NIH issue. It is an issue that is much broader within our society. It is an issue for the Congress; it is an issue for the White House. But it is not an NIH issue.[161]

Robert Gellman worked on a policy report in the wake of the hearing. His report was ready by April 1992.[162] Rep. Wise sent it to the Secretaries of Health and Human Services (for NIH) and Energy, accompanied by a cover letter concluding that "the existing ethical, legal, and social implications (ELSI) programs at the National Institutes of Health and Department of Energy are principally designed to support academic research. . . . these programs are not capable of developing or presenting policy recommendations and there is no existing policy process. . . ." The letter went on to recommend that NIH and DOE "jointly establish an Advisory Commission on the Ethical, Legal, and Social Implications of the Human Genome Project" and hammered home the point urging that it be established *immediately* and that it be in operation within four months (emphasis in original).[163]

The report was a distillation of successful federal commissions, including not only the National Commission and President's Commission in bioethics but also the Advisory Committee on Automated Personal Data Systems (1972–1973), the Privacy Protection Study Committee (1975–1977), and presidential commissions on AIDS.[162] (Notably, it did not describe the less successful BEAC or other bioethics efforts of the late 1980s.) The report passed lightly over the grants program mounted by NIH and DOE. These were immensely useful and likely to contribute more than the committee might appreciate. Had the President's Commission and National Commission had a fertile field of grant-supported investigators to consult with, their harvest of new ideas would likely have been richer and their job easier. Moreover, the agencies could farm out policy analysis on specific topics, even if they could not conduct it themselves. The Institute of Medicine, for example, was pursuing just the kind of systematic policy analysis of genetic testing that the committee called for, through a contract with NIH and DOE.

The committee's point was nonetheless valid. The thrust of the NIH and DOE programs was indeed on academic research, and that did not equate to policy analysis. If Congress wanted policy analysis, it might have to craft a new instrument. The ELSI program was established to thwart misuse of genetic information, and that would require policy analysis. A structure to sustain that analysis was needed.

NIH's initial response to the letter from Wise was not promising. The proposal sent to the department was for a structure seemingly modeled on the fetal tissue transplantation research panel. This corroborated initial press reports of the policy analysis unit being established in director Healy's office.[164] Daryl Chamblee was hired from the Washington law firm of Steptoe & Johnson to head the bioethics component.[165] Chamblee had been interested in bioethics for several years, centered on work with the Columbia Hospital for Women. The ethical analysis component would be part of a general science

policy shop answering to deputy director Jay Moskowitz, who had overseen the fetal tissue transplantation research panel. The proposal was to have the ELSI advisory commission on the genome report to the NIH director's advisory committee, with staffing from the staff pool of the director's science policy analysis center. House subcommittee staff were unimpressed with the proposed structure, mainly because it lacked the reporting autonomy they believed necessary to function effectively.

The NIH draft strategic plan stated that "the aim of confronting these social, legal and ethical problems in research is not to promulgate new regulations or create another layer of research review. Rather, the aim is to provide the research community with relevant guidance for the conduct of research and to assure the public's understanding of the social benefits and consequences of science."[166] There were indeed science policy questions that might be handled well within the NIH, centering on peer review, standards for scientific research, and administrative process. For such questions, the direct link into the director's office, and thence into the administrative hierarchy, would be a great advantage. Other questions that touched on broad social policy well beyond the confines of NIH, but directly linked to science policy decisions, would require an analytical engine on a separate track. A commission's credibility in addressing such questions would hinge on independence from NIH (or DOE), and its influence would derive from reporting directly to Congress, the President, and the nation, free of bureaucratic clearance procedures.

While the House subcommittee was crafting its report, the Senate was also interested in bioethics, but from an independent starting point. Senator Mark Hatfield had long been concerned about advances in genetics. In 1983, he introduced Jeremy Rifkin's resolution and "theological letter" on germ line gene therapy.[94] In that statement, he noted how he had visited Hiroshima soon after the atomic bomb was dropped. He worried about whether technology was not racing ahead of the capacity to control it, and worried specifically about genetics. In 1981, the biotechnology company Cetus raised $120 million in the fifth-largest public stock offering in history. Genetic advances might produce a Brave New World, and "return to slavery is possible unless public and private institutions enter into a dialogue with vigor."[94]

In 1989, Senator Hatfield was the only member of Congress, other than Biomedical Ethics Board members, to support the Biomedical Ethics Advisory Committee. He viewed its work on human genetics as important, and said so in support of funding for BEAC before the Senate Appropriations Committee, on which he sat as ranking minority member.

In April 1992, Hatfield's concerns were rekindled by an NIH effort to patent 2,700 DNA sequences (see Chapters 19 and 20). He announced an intention to call for a moratorium on patenting DNA sequences and genetically engineered animals until a study of the ethical issues could be conducted. He rose to address the Senate:

The research conducted by the National Institutes of Health is, in my opinion, one of the Federal Government's greatest gifts to the Nation; it is the gift of improving the human condition by alleviating the pain and suffering associated with disease. As deep as my respect is for the medical research community, Mr. President, I stand here today deeply concerned about the future use of research findings."[167]

Senator Hatfield intended to propose that BEAC be brought back to life, with a new congressional board and new BEAC members, to conduct a study of whether patents should be issued. He contemplated introducing an amendment to impose a moratorium on such patents until the study was complete. Senators DeConcini and Kennedy, working with Senator Domenici, cut a deal with him. Hatfield expressed his concerns on the floor, but did not offer his amendment. In return, Senators Kennedy and DeConcini agreed to host hearings before the Judiciary Committee, on patenting issues, and in the Labor and Human Resources Committee, on other ethical and social issues related to genetics.[167] Out of this agreement, the Office of Technology Assessment was requested to begin a project on DNA patenting and to hold a "bioethics summit" to review the history of bioethics commissions, with an eye to laying out options for future efforts. OTA released its report in fall 1993.[169]

Hatfield's proposed amendment provoked a frenetic lobbying effort against it.[168] A letter from Louis Sullivan, Jr., Secretary of Health and Human Services, argued that reconstituting the BEAC was a redundancy, once again betraying a confusion between the research program sponsored by NIH and a capacity for conducting policy analysis of that research, similar to the President's Commission or National Commission:

Much of the information that this board would collect is already being collected in other venues. The National Center for Human Genome Research has devoted approximately 5 percent of its budget to the study of ethical, legal, economic, and social problems associated with the mapping and sequencing of the human genome.[170]

The point about the value of the research effort was true, but the incapacity to synthesize it into policy was clearly not appreciated. As the genome project neared the end of its fifth year, the social issues raised by the coming deluge of genetic information continued to fester. NIH and DOE mounted research programs to support policy analysis and to provoke a broad debate. These programs were unprecedented in science, and were auspicious institutional innovations within both agencies. At the same time, however, the agencies failed to take account of the process, staffing, and funding requirements to nurture policy analysis, in particular the general and principled guidance that might assist Congress to craft rules of law. A renewed interest in bioethics was clear in both the House and Senate. Because the executive branch failed to appreciate the chasm between the ELSI research program and policy analysis, it invited Congress to fill the gap.

18

Wizards of the Information Age

One day in 1950, the Polish mathematician Stanislaw Ulam had an idea about how to set off a thermonuclear fusion bomb, or hydrogen bomb. His idea became reality with the first explosion of a fusion device in October 1952.[1] Ulam came to the United States in December 1935, at age twenty-six, at the invitation of John von Neumann, who later became his link to the Manhattan Project. Ulam went to Los Alamos in February 1944, several months after the boys' school there was commandeered to become the scientific hub of the project. When the war ended, Ulam moved to the University of Southern California, where he felt intellectually isolated. According to Gian-Carlo Rota, a longtime colleague of Ulam's, "suddenly he found himself in the middle of an asphalt jungle, teaching calculus to morons."[2] He weathered a bout with encephalitis, which left him with a distaste for Los Angeles and a persistent insecurity about whether his mind worked as well as it had before. A fascination with the workings of the brain was perhaps the most significant legacy of Ulam's brush with death.

Ulam returned to Los Alamos in May 1946 and began to work on the next secret Los Alamos project, a fusion bomb, or "Super." In 1949, the Soviet Union detonated a fission bomb, similar to those exploded over Hiroshima and Nagasaki. This revived Edward Teller's "Super" project. Whether the United States should proceed to produce a fusion bomb more powerful than the fission bombs used at the end of the war was a central policy question of the day. Scientists debated its feasibility, and they joined others in questioning the wisdom of such a project. The Soviet successes fueled paranoia in Washington and tipped the political balance toward Edward Teller's position of enthusiastic support for a fusion bomb: President Truman plunged into developing a more powerful weapon, and Ulam was where most of the action was.

Ulam's first contribution to the hydrogen bomb was to show that Teller's scheme would not work.[3] Ulam met Teller during the Manhattan Project, and the two became linked in a collaboration of immense historical significance, but leavened with mutual distaste at the personal level. Rota ascribed Ulam's enthusiasm to personal motives: "Stan Ulam was out to get him [Teller] by proving that his plans for the new bomb would not work."[2] Two years of

elaborate and tedious hand calculations by Ulam and C. J. Everett were corroborated by one of the first major uses of a digital computer, under von Neumann at Princeton, using a different modeling method.

Having shot Teller's idea down, Ulam floated one of his own. "Adding insult to injury, Stan, in a sudden flash of inspiration, came upon a trick to make the first hydrogen bomb work."[2] Ulam's notion was "an iterative idea" that he developed with Teller into a report that "became the fundamental basis for the design of the first successful thermonuclear reactions and the test in the Pacific called Mike."[1] These were two separate events, with the first test of a sixty-five-ton device named Greenhouse on Eniwetok Atoll in May 1951, and the Mike test in November 1952.[4] Ulam's critical role in the fusion bomb is highlighted in documents recently brought to light.[5]

The mind that devised the scheme for the hydrogen bomb also spun out ideas central to the mathematical analysis of DNA sequences. Ulam was drawn into biology by his younger colleagues at Los Alamos, particularly George Bell and Walter Goad, and by Leonard Lerman and Theodore Puck from Colorado, who had collaborative ties with Los Alamos. Lerman later became a wizard of technological development in molecular biology, and Puck one of the major figures in gene mapping and tissue culture of mammalian cells (growing cells from the body in petri dishes, much like bacteria or fungi).

Many roots of computational biology that began to blossom in the 1970s and 1980s trace to the group surrounding Ulam at Los Alamos. To analyze the information contained in the DNA code, one needed a metric, a formal measure of the similarity between two DNA sequences. Ulam suggested that the metric might be formulated as the least number of changes (substitution of one base for another or addition or deletion of a base) necessary to transform one sequence into another. This idea emerged from a conversation between Ulam and Temple Smith in 1968, soon after Ulam moved to Colorado. Ulam sketched these ideas in a 1972 paper.[6] Smith and Ulam worked with William Beyer and Myron Stein of Los Alamos to extend these ideas in 1974.[7]

A rigorous measure for sequence similarity fed into a growing movement to analyze protein and DNA sequence data using mathematical tools. The mathematical work built on several comparative studies in biochemistry and molecular biology. Emile Zuckerkandl and Linus Pauling unexpectedly found in 1962 that the amino acid sequence information in proteins could be used as a "molecular clock" to trace evolutionary history. They published the seminal paper in the field three years later.[8] Walter Fitch and E. Margoliash similarly constructed an evolutionary tree based on similarities among amino acid sequences of cytochrome c proteins in different species.[9] During the mid-1960s, Margaret Dayhoff of Georgetown University began to assemble an *Atlas of Protein Sequence and Structure*.[10;11] Dayhoff devised rules for calculating sequence similarities among proteins, based on the chemical similarity of amino acids.[12] Her catalog of proteins was organized according to functional and

evolutionary types. Meanwhile, work on DNA sequences paralleled protein sequence analysis.

In 1970, Saul Needleman and Christian Wunch developed an algorithm, easily adapted to computers, to compare the similarity of two sequences, basically by counting how many steps it would take to transform one into the other.[13] This method was quite useful, but was not mathematically rigorous until Peter Sellers of Rockefeller University formalized Ulam's idea of a metric in 1974.[14;15] Temple Smith and Michael Waterman generalized the measure in a mathematically rigorous way that could account for small insertions and deletions.[16]

Mathematicians and statisticians thus greatly expanded the sophistication of techniques to derive meaningful information from DNA and protein sequences.[17] Indeed, the originator of the DOE genome project, Charles DeLisi, came from this field of mathematical biology. His mind was thus prepared for the notion that DNA sequence information could become the raw data for an entirely new field of theoretical genetics, in which the genome project would be a major step.[18]

The linear sequence of information in the order of amino acids constituting a protein, or of nucleotides making up a strand of DNA, was a natural target for computer analysis. Molecular techniques came of age at just the time that digital computers were becoming faster, cheaper, and more portable. "Tools needed to store, search, and analyze the new data grew up alongside the tools necessary to generate the data."[11] Through the 1970s, a small group of individuals began to realize that computers and sequence information were a natural marriage. Bride and groom struggled to overcome vast cultural differences. Computer scientists and molecular biologists traced their lineage through different tribes, with vastly different norms, and only a few hardy souls could converse in both languages and command respect in both communities. The databases that stored sequence data became their meeting ground.

A meeting held at Rockefeller University in March 1979 was a watershed. According to one participant, "no one questioned but that computers and sequence data were made for each other. Transmitting a long, seemingly random sequence of four letters from one person to another without errors is hardly possible except by putting the information on a computer-readable medium. The need for a data bank was in the air."[19] The meeting brought together an eclectic collection of people interested in applying computers to molecular biology. There were groups that had worked on the NIH-funded PROPHET project in Boston, which grew up around those associated with MIT and the private firm Bolt, Beranek & Newman (BBN). Two projects that brought together computers and chemistry at Stanford—SUMEX (for medical applications) and Molgen (for organic chemistry)—were also represented. Temple Smith and Michael Waterman attended from Los Alamos. The two had not worked together before, but both returned from the meeting enthu-

siastic about the idea of a database and DNA sequence analysis center at Los Alamos.[20;21] Five other groups were possible candidate sites for a database: the group surrounding Dayhoff at the National Biomedical Research Foundation, the MIT-BBN group, the Stanford group, another group led by Olga Kennard and Frederick Sanger in Cambridge, England, and a group at the European Molecular Biology Laboratory (EMBL).[11]

By the following April, several groups had assembled pilot DNA sequence repositories that were discussed at a meeting in Schönau, Germany. There was further discussion about the need for a national or international database, and consternation among Americans about inaction at the National Institutes of Health. A workshop was held at NIH on July 14, organized by Elke Jordan of the National Institute of General Medical Sciences (NIGMS). Within a month, a flurry of proposals came in to NIH for databases, DNA sequence analysis methods, or both. On October 26, Elke Jordan convened an *ad hoc* advisory group, which on December 7 elaborated a plan. A public national database for DNA sequence information was to be established as Phase I, followed by a center for development of analytical methods in Phase II. Phase I would establish the capacity to collect data, Phase II would develop mathematical and computational methods to analyze the information. On April 2, 1981, NIH released a "sources sought" document, inviting expressions of interest in applying for funding. Meanwhile in Heidelberg, Gregg Hamm began operating the EMBL Data Library, thus getting a six-month jump on American efforts.[22]

Late in 1981, NIH requested contract proposals for the database part, or Phase I. Phase II was dropped because of cost, politics, and lack of clarity about what a DNA analysis center would be.[19] Three proposals were sent to NIH. One came from Dayhoff's group. Los Alamos was part of the other two. In both proposals, Los Alamos was the collection and storage center, but the distribution plans were different. One was a collaboration with a company formed out of the Stanford group, IntelliGenetics; the other involved the MIT-BBN group. NIH announced its award of the contract to the BBN–Los Alamos group on June 30, 1982, and the database began to operate in October.[11] An August meeting on computational biology in Aspen brought together many members of this small community for two weeks,[23] in the wake of NIH's announcement but before GenBank began to operate. David Lipman there introduced his idea of a "hash code," a way of aggregating data to expedite searches of massive databases.[11;24;25] (Six years later, Lipman became director of the National Center for Biotechnology Information at the National Library of Medicine.) Margaret Dayhoff died soon after the workshop.

A different part of NIH, the Division of Research Resources, later funded BIONET at IntelliGenetics, which grew out of the Stanford group's work. This was initially to serve both as a software resource and as a center for development of analytical methods, overlapping with the Phase II plan abandoned by NIGMS. The BIONET grant was not renewed in 1989. It linked small laboratories to software they otherwise would lack, but never developed

into the major center for devising new methods that some had hoped.[11;26] Indeed no systematic program to cultivate new analytical methods for molecular analysis ever developed, in the judgment of many, until the Human Genome Project came along to shine a spotlight on the problem again.

GenBank and the EMBL Data Library fell quickly into arrears. During the early years, most entries were typed in by hand at GenBank or EMBL. The two database centers divided journals into two roughly equal sets and split responsibility for entering sequence data. The DNA sequence databases were quickly inundated by the flood of data. In their first four years, they grew twenty-five-fold, far faster than projected. Yet GenBank was funded by a five-year budget that was already insufficient two years into operation. In mid-1986, only 19 percent of the sequence data published in 1985 were entered.[22] Some sequences were more than two years old before entry, and the databases contained barely half the sequence information published to date.[27] At an acrimonious meeting of the GenBank advisory committee, scientists were divided over how to cope with the emergency. The result was a new policy of entering only raw sequence data, leaving out most features known about the sequence. The number of "unannotated entries" rose quickly, and began to drop only in 1988, after a new contract substantially increased funding for GenBank.[28]

In this forced marriage of computer and DNA, there was little time to enjoy a honeymoon. GenBank was a patched-together raft riding out a tsunami. As originally proposed in December 1989, GenBank was to build on a data structure known as a relational database. In essence, data would be organized into tables. The rows of the table would be individual entries—the sequence data from a gene or chromosomal region. The columns would be biological features, information about the DNA's region of origin, information about the gene, the species of origin, and other details relevant to interpreting the sequence.[29] The advantage of the relational framework was its logical structure, which also simplified search strategies. As actually implemented, GenBank instead stored the data as a "flat file," basically units of text with punctuation marks not organized into tabular form. The computer and storage hardware were also far less powerful than originally proposed.

Both GenBank and EMBL Data Library were politically complicated. GenBank was operated at a DOE-owned national laboratory but funded by a group of NIH institutes, the Department of Defense, the National Science Foundation, and the Department of Energy. EMBL's database was funded by various European governments and the Commission of the European Communities. Both databases were struggling to secure resources, very much stepchildren in the biomedical research family. Molecular biologists had little notion of the difficult issues facing any large public database. They were impatient to use the data, but unenthusiastic about paying enough for its storage. The genome debate was a glass slipper for the databases, making apparent how important they were to the future of biology, and making them into Cinder-

ellas within their respective bureaucracies. GenBank's second five-year contract, negotiated in 1987, had a budget of $17.5 million, compared to the $3.5 million contract that took effect in October 1982. In fiscal year 1993, GenBank prepared for another transition, as its management was slated for transfer to the National Library of Medicine.

The new reliance on computers and communications technologies melted yet another group into the genome pot. Databases, computers, and mathematical algorithms proved as important as DNA sequencing, cloning, and other more obviously biological techniques. As geneticists produced a deluge of data during the 1990s and beyond, those who understood hardware and software would play an increasingly important role.

The multitude of genome research programs in the United States, Japan, the USSR, and Europe all promised to generate massive amounts of data. The flow of information became the focus for negotiations among scientists and science administrators because this flow was of benefit to every nation. The inherent need to ensure smooth flow of data and the benefits of ensuring some consistency of interpretation necessitated extensive international collaborations that nucleated around genome databases, as databases became brokers for international information exchange.

At a 1987 meeting in Heidelberg, the DNA Database of Japan (DDBJ), funded by the Science and Technology Agency, was brought into the fold, joining the EMBL Data Library and GenBank. DDBJ had served as a distribution node since 1984, but agreed to begin gathering data for Japan and other parts of Asia. An international advisory committee, chaired by Dieter Soll of Yale University, met in February 1988. The advisory committee berated the database managers in stern language, urging them to make their databases compatible, so that editing, annotation, and corrections entered in one database did not have to be repeated at the other centers.[30]

The features that made databases complex to maintain politically, with their disparate and multicentric funding structures, also made them natural foci for organization at the international level. Having already solved the problem of gathering funds and scientists together, they were natural centers to coordinate other research activities. An odd *Nature* editorial appeared soon after the Alberts report of the National Research Council was released in February 1988. It urged an expeditious genome project, but cautioned against organizing a biological Apollo project. It tipped its hat to databases:

> If the databanks were a necessity when they were first created five years ago, improved versions of them are surely even more necessary now. . . . This is where the organization-building should begin. . . . The job should be tackled internationally so as to win the greatest benefits from the data gathered in widely scattered laboratories.[31]

But *Nature* was unwilling to use its clout to promote the flow of data into databases. John Maddox, editor of *Nature,* balked at the notion that journals, least of all his, should play the role of traffic cop. Lennart Philipson noted

Maddox's inconsistency in advising against formal coordination of the genome project while promoting an "internationally coordinated mega-databank."[32] Philipson noted that EMBL, GenBank, and DDBJ were jointly "close to an international data source in biology" and urged that *Nature* join the journals mandating sequence submission to databases. *Nucleic Acids Research,* the *Journal of Biological Chemistry,* and other journals adopted policies requiring such submission, but Maddox held out noisily. He argued against coercive editorial policies again in 1989, asserting that some laboratories did not have ample computer facilities, that sequence databases were inaccessible in the Soviet Union, and that it was not the role of editors to serve as enforcers.[33]

Richard Roberts of Cold Spring Harbor Laboratory countered in a letter to *Nature* that journals were uniquely positioned to ensure timely submission of data to databases.[34] Sequence data were essential to verifying statements in articles, and the only meaningful way to interpret DNA sequence data was to use a computer: "A computer is every bit as necessary as a centrifuge to today's molecular biologist." Roberts called Maddox's arguments "a potpourri of excuses for inaction."[34] Thomas Koetzle noted that the crystallographic research community faced similar dilemmas and favored mandated submission, with the option of one year's delay from time of publication to public release.[35] As EMBL weighed in,[36] Maddox capitulated, but his was not an unconditional surrender.

Maddox argued, "Difficulties arise when contributors are asked to satisfy conditions that have *nothing to do* with the content of what they have to say" (italics added).[37] Maddox's point was strained, to say the least. Conclusions in the papers were based on the sequence data in question or there was little point in publishing them. Sequence data were of little use as letters on a page without the ability to compare to other sequences or to analyze them with computer software. The problem was even more acute if DNA sequence data were merely contributory to a publication. If the sequence data were not published and never contributed to a database, how would others know the reliability of the work? How would others compare their sequences against the new sequence? Maddox could not imagine why his journal "founded 120 years ago to bring the record of research to a wide audience, could fall in with the idea that its readers' appreciation of what they read will hang crucially on the accessibility of a databank in Heidelberg, Los Alamos, or Mishima."[37] *Nature* depended instead on mail circulation, which one might doubt was as widespread in the 1870s as computers were in the 1990s. Thomas Kuhn observed that scientific revolutions sometimes required dinosaurs, the waning generation of scientists, to die off before being supplanted by mammals.[38] Add journal editors kneeling before the altar of the printed page, and the printed page alone, to the list of species headed for extinction. Where there was DNA sequence information, there would be computers.

Sequence databases were not the only ones established to deal with genetics. Another group of databases centered on gene maps and genetic dis-

eases. The most famous among these grew out of human genetics. Victor McKusick at Johns Hopkins began to keep track of genetic disorders and variants in 1960. In 1962, he published the first catalog of human genes, a hundred-page compilation of data on the X chromosome.[39] He also monitored other chromosomes, and produced the first edition of his book *Mendelian Inheritance in Man* in 1966.[40] McKusick published seven editions of his book, and then put his list of disorders and genes on-line in 1987, in a collaboration with the National Library of Medicine and with funding from the Howard Hughes Medical Institute. McKusick continued to publish the book version every two years, making the data more portable and also surveying the field in a foreword of increasing breadth and length with each edition.[41;42] The book version became a periodic snapshot of the computer database, "arguably the most valuable compendium of human genetic disease information currently available."[43] The database was an "encyclopedia of genes" in the human genome.[41] By the ninth edition in 1990, the catalog contained 37,987 references written by 54,623 authors, and yet it covered "perhaps only 5 to 10 percent or less of all the structural genes of man."[42]

Beginning with the first human gene mapping meeting in New Haven, Connecticut, in 1973, those engaged in mapping human genes began to catalog their progress at periodic meetings. The data pooled at these human gene mapping workshops cried out for consolidation into a database. Frank Ruddle and others at Yale University stepped forward and began to catalog the information about gene location, chromosome structure, literature citation, and other relevant information. The Human Gene Mapping Library was cross-tabulated to McKusick's catalog of genes and disorders.

Yale's Human Gene Mapping Library was supported by an NIH grant initially. When the grant was up for renewal, an NIH review panel recommended against continued funding, citing problems with the underlying technical approach and other factors.[20] HHMI stepped in to preserve the database with several years' funding, starting in 1985. This arrangement persisted until 1989, when HHMI decided to move toward a system that was easier to use and whose underlying database structure was more up to date than the SPIRES system (an IBM software package) used at Yale. HHMI shifted support to Peter Pearson, who was recruited to Johns Hopkins from Leiden to run a new Genome Database at the Welch Library, already home to McKusick's catalog of human genes.[44]

The Genome Database was for gene mappers and contained information on genetic linkage maps and physical maps. The focus was on gene location on the chromosomes, with information about genes, disease-associated regions, and markers. The Genome Database released a mission statement in September 1989[45] and debuted at Oxford in September 1990, at a meeting to prepare for the international Human Gene Mapping Workshop the following year in London.[46] By January 1991, three thousand users were registered from around the globe and two thousand people logged onto the database each

month.[47] HHMI funding established the Genome Database, but government funding would be necessary to make it permanent. Through 1991 and into 1992, NIH and DOE negotiated funding for it.[48] Self-supporting centers were established as nodes in the UK, Australia, and Germany, and establishing a center in Japan was a part of the 1992 genome program in Japan.[49;50]

The information in the Genome Database largely complemented the contents of GenBank, which stored information about DNA sequence; and also the McKusick catalog, which focused on pedigree information, clinical description, and mode of inheritance. For some applications, melding information from the three different sources could be difficult. It was not possible to retrieve DNA sequences known to be taken from a particular chromosome region, for example, and yet this was a common need for those seeking mapped genes.[51] Similarly, the data on physical maps under construction were not initially integrated into either the Genome Database or GenBank. Devising ways to link the various databases and to consolidate information derived from disparate mapping techniques loomed as a major objective for software development.[51] Jacqueline Courteau, who wrote the appendix on databases for the 1988 OTA report, revisited the topic in 1991 in a pull-out section of *Science*'s annual theme issue on genome research.[52] The databases had grown enormously in three years, and with this growth came political and intellectual complexity in linking them.

Databases became an essential element in the pursuit of genetic knowledge. There were many relevant databases, however, and they were managed differently, located throughout the world, used different software and hardware, and contained different types of information. Making the databases more readily accessible and linking them to analytical software packages to assist in analysis became another set of problems to solve. The National Library of Medicine (NLM), through the National Center for Biotechnology Information, became one integrative force. GenBank was moved administratively from the National Institute of General Medical Sciences to NLM in 1992. There was also a minor industry devoted to improving database access and analytical software. GenBank had always been housed at Los Alamos National Laboratory, but the information had been distributed through a commercial firm (Bolt, Beranek & Newman from 1982 to 1987, and then IntelliGenetics from 1987 to 1992). Several small firms had grown up making software to analyze genetic data, and many sold their software with somewhat modified packages of GenBank data. The transition back into the federal fold provoked a major controversy that endangered these companies. They retaliated by threatening NLM's budget.[53]

Some of the software vendors believed that NLM was developing competitive software with a heavy subsidy, undercutting the markets for their products. Several of the software companies' directors complained to David Lipman, director of the NLM effort. Their discomfiture began in 1989 and 1990, when

discussions about moving GenBank were being negotiated within NIH.[54] They hired a lobbyist, who taught them how to go for the jugular. On June 18, just weeks before the appropriation figures would be finalized, they sent a letter to William Natcher, chair of the subcommittee that appropriated NIH funds, including the NLM. Staff for the subcommittee were concerned that federal dollars would go for research that could be done by private industry; the message was clear to NLM that its program was in serious jeopardy. Matters had gone further than the instigators intended. Moreover, they had failed to inform other companies that also had a stake in the outcome, and these firms then wrote letters to Natcher disavowing the original letter.

The conflict stemmed from disturbing the sociology of software development. This was territory where both federally sponsored investigators and private vendors grazed, and there was bound to be continuing tension. There was an enormous amount of work to be done, and there was money to be made. Much like the looming conflict over patenting of DNA sequences, the question of who would control the territory was unsettled. Analytical software and database access were among the many disputed borders within the genome project. The companies and NLM reached an agreement for the time being, but the issue would surely surface again.

The purpose of the databases was to pool data from disparate sources, so that information would be readily available to others who could use it. Indeed, if the goal of the genome project was to construct maps, those maps were inevitably built from information contributed to databases. Maps were irreducibly collective endeavors. Once made, they enabled analysis of information in an entirely new way. The analysis of all the data spawned a new field. Computers and mathematical techniques were turned loose on the data to construct theories of biological structure and function. The first glimmerings of Walter Gilbert's dream, a theoretically driven science of molecular biology, could be seen on the horizon.

Databases were tools to find and to understand genes. Mathematical methods were an important part of making the stored information biologically meaningful, and this circled back to the interests of Stanislaw Ulam's heirs.

One cluster of activities centered on the interpretation of genetic linkage—statistical methods for relating the inheritance of characters to physical locations on the chromosomes. Analyzing pedigrees for statistical evidence of gene transmission was a complex art, and a small core of scientists traversed the treacherous trail. A few biologists comfortable with both the molecular biology laboratory and mathematical reasoning became the luminaries of a small and highly mathematical field, devising new ways to find genes floating on oceans of data.[17;55–60] Entirely different fields of mathematical genetics flourished, for example the analysis of amino acid sequence patterns in proteins, used to predict their structure and to sort protein regions into classes with

similar functions.[61–65] Mathematical tools were also applied to physical mapping. Eric Lander and Michael Waterman, for example, made a straightforward mathematical model of how cloned DNA fragments could be assembled into physical maps, thus providing a theoretical benchmark against which those constructing maps could compare their experimental results.[66]

Mathematical methods were clearly destined to play an increasing role in understanding the complex phenomena of biology. It became clear that sequence comparisons would become a powerful tool in assessing biological function. Russell Doolittle and his collaborators shocked the world of molecular biology by finding a sequence similarity between the *sis* oncogene and a cellular growth factor.[67] The oncogene came from a cancer-causing virus of primates. The growth factor was one of many that transmitted signals controlling cellular functions. The growth factors bound to the outer surfaces of cells and were translated by cellular machinery into a cascade of events, most often leading to proliferation or differentiation of cells. Doolittle's finding of a structural similarity was entirely unexpected and came from simply scanning sequences in a database. He had not determined the sequences, nor had he done the underlying biochemistry that illuminated the two proteins' functions. His contribution was to notice that two proteins hitherto thought entirely unrelated were structurally similar, and likely to be functionally related. By this stroke, he discovered a biological relationship that had eluded those working on the biochemistry of the oncogene protein and other groups focused on the growth factor. A computer comparison thus unified two separate subfields. The receptor for another growth factor and a different oncogene were found related a year later, lending credence to theories that linked cancer to aberrant control of cell growth.[68] The importance of building databases to enable the detection of such similarities began to dawn on molecular biologists, and the analytical tools to detect the similarities developed apace.[69]

In a 1985 report, a committee of the National Research Council (NRC) emphasized the importance of computational methods.[70] One spinoff of the report was a month-long meeting, the Matrix of Biological Knowledge Workshop, at the Santa Fe Institute from July 13 to August 14, 1987.[71] Another NRC committee released a report in 1987, emphasizing the importance of computer models to understand the structure and function of proteins, DNA, and RNA.[72] The theoretical methods that had so long brought coherence to physics and chemistry began to seep into the crevices of molecular biology, which for a generation had been an almost purely experimental science.

Many molecular biologists were uncomfortable with the shift of power to the mathematicians and analysts. Some even resented forays such as Doolittle's into their territory. Why should he be able to publish a major discovery that came from just sitting at a computer terminal? That wasn't biology, was it? From 1950 to 1980 it had not been molecular biology; beginning in 1983, it was. The intrusion of computers into molecular biology shifted power into

the hands of those with mathematical aptitudes and computer savvy. A new breed of scientist began to rise through the ranks, with expertise and molecular biology, computers, and mathematical analysis.

In 1860, Charles Darwin's champion, Thomas Henry Huxley, debated the Bishop of Oxford, Samuel ("Soapy Sam") Wilberforce, before the British Association for the Advancement of Science.[73] Before a packed room of seven hundred eager to watch a rhetorical bloodbath, the bishop made a major tactical error while belittling the theory of evolution. He asked whether Huxley traced his descent from the apes through his mother or his father. Huxley responded, in a riposte taught to several generations of biology students, "If the question is put to me 'Would I rather have a miserable ape for a grandfather, or a man highly endowed by nature and possessed of great means and influence, and yet who employs these faculties and that influence for the mere purpose of introducing ridicule into a grave scientific discussion,' I unhesitatingly affirm my preference for the ape."[73;74]

Debate about human evolution in the ensuing century and a third was a series of similar imbroglios. Liberal theology incorporated science by interpreting religious texts as analogical rather than literal. Science was accepted as the factual base, and theology the spiritual guide. Fundamentalists could not abide such concessions, and thus brooked direct confrontation with science. Bad blood coursed between biology and theology when evolution was the topic. Molecular genetics made matters worse.

In 1975, 115 years after the Huxley-Wilberforce debate, Mary-Claire King and Allan Wilson from the University of California at Berkeley published a paper synthesizing various analyses of DNA and protein similarities between humans and chimpanzees. Soapy Sam got horrid news. Genetic similarities between man and chimp were as close as sibling species of mammals (various members of the cat family, or canines, for example). King and Wilson noted that "the average human polypeptide [protein] is more than 99 percent identical to its chimpanzee counterpart."[75] Differences in DNA sequence were somewhat greater, as expected, but genetically speaking, the two species were amazingly similar.

For centuries, humans led by the clergy had struggled to distance themselves from the rest of creation, to build a qualitative wall between themselves and the other creatures of the animal kingdom. Humans placed themselves in a separate genus and family from other hominid apes. A part of this was chauvinism, well documented in separatist theology and philosophy. The classification scheme also acknowledged, however, enormous biological differences. Humans alone spoke, had written language, engaged in moral discourse, and built civilizations. The genetic similarities in the face of such dramatic anatomic and behavioral differences led King and Wilson to postulate that the changes must affect regulatory elements, perhaps those controlling the expression of genes during skeletal and brain development. They invoked subtle

changes in when and how genes were expressed to bridge the chasm between genetic similarity, on the one hand, and behavioral and anatomic difference, on the other. The structural alterations would affect not which genes (and proteins) there were, but when they turned on and off, how long they acted, and how much they produced.

The genetic similarity of man and chimp was but one of many results that came from applying molecular methods to evolutionary biology. In the related field of paleontology, Wilson and colleagues used DNA sequence data from mitochondria (subcellular structures with a residual genome of their own) to trace the origin of modern humans to Africa several hundred thousand years ago.[76] The initial analysis proved more tenuous than imagined, subject to foibles of computational strategy, and suggested alternatives to human populations radiating out of Africa.[77] The use of DNA sequencing as a tool for paleontology was no longer in doubt, however, and augmented the traditional methods of bone analysis and archaeology. Luigi Luca Cavalli-Sforza and his colleagues at Stanford analyzed data from several chromosomal locations and found that DNA-based data corroborated archaeological and linguistic reconstructions of human migratory patterns.[78] Molecular biology invaded the fields of evolutionary biology, paleontology, and population genetics, yielding a wealth of data that awaited the new technologies for analyzing DNA structure.[79]

Comparing protein sequences among different species revealed several distinct classes of proteins.[80] Some were quite ancient, and were shared with many bacteria and other primitive organisms. These proteins were involved in metabolic processes essential to all life forms on earth. At the other end of the spectrum were proteins of more recent vintage, which showed evidence of having been assembled in bits and pieces by exchanges of blocks of DNA. Other proteins fell in between. Astronomers had long accustomed themselves to looking at the distant past. Their telescopes and detection instruments often captured light that left its source billions of years ago, so direct observation of distant objects was the same as looking into the remote past. By studying sequence data, the detritus accumulated over the course of evolution, biologists could now similarly glimpse into the distant biological past.

Analysis of DNA also permitted the study of contemporary human populations. Luca Cavalli-Sforza and Walter Bodmer surveyed variations among human populations in a 1976 textbook, *Genetics, Evolution, and Man,*[81] published at the dawn of the recombinant DNA era. Using DNA analysis and protein sequence analysis, the historical migrations of human populations in prehistoric periods could be inferred. Results from DNA analysis corroborated in general outline the conclusions from linguistic analysis, through the study of how languages were related to one another. Most of the conclusions remained the same, but the base of data was greatly expanded, and there was a promise of greater precision in the future as the genetic gold was mined. As methods improved, however, one factor necessary to assess human genetic

variation diminished. The optimal populations to produce useful data, those that had been relatively isolated and geographically stable for a long time, were either dying off, being assimilated into surrounding populations, or migrating in the face of war and internal conflict. Anne Bowcock and Cavalli-Sforza noted in a 1991 article:

A number of populations of considerable interest are rapidly disappearing. Large geographic areas are being exploited and developed, changing rapidly and irreversibly the tribal worlds that still survive in every continent. The loss of traditional lifestyles destroys established communities, and their Diaspora makes it practically impossible to sample them. It is only from knowledge of the gene pools of these populations that we can hope to reconstruct the history of the human past. But humans are an endangered species from the point of view of genetic history.[82]

The need to secure the resources necessary to interpret human evolutionary history and to interpret contemporary data on population genetics brought together groups long known for word-to-word combat in the scientific trenches. A series of documents called for international mobilization to sample aboriginal populations around the globe, so that genetic variation could be assessed now and in the future as better methods developed.[82–87] UNESCO agreed to assist in the effort at a June 1991 meeting in Paris, and HUGO appointed a committee to set forth the appropriate scientific strategy. On June 5, 1992, the National Science Foundation, DOE, and NIH funded a $150,000 two-year grant to Marcus Feldman, working with Luca Cavalli-Sforza at Stanford, to support three workshops intended to plan at a much larger subsequent effort.[88] The overall project might cost more than one hundred times as much and would involve sampling populations from around the globe in search of our collective genetic history. Allan Wilson died in 1991, but his ideas did not.

Charles Darwin founded the science of biology on a theoretical footing. He closed the most important book in biology, *The Origin of Species,* on a philosophical note:

From the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved.[89]

The genome project has its sights aimed at the biological stuff that mediated the process of evolution. DNA was the structure that conferred inheritance and permitted small incremental changes to pass into new generations, while ensuring sufficient inherited stability to carry on life. Over the millennia, the instructions in the genetic code were modified not only in humans but in every living thing on the planet. The genome revealed relics of this evolutionary history. The biological revolution had, in many senses, been a continuous

one over more than a century. Another major revolution in mathematics was of more recent origin.

At the turn of the century, Alfred North Whitehead and Bertrand Russell attempted to place mathematics on solid footing, to build its foundation on intellectual bedrock. Together, Russell and Whitehead wrote *Principia Mathematica,* one of the intellectual monuments of this century,[90–92] a culmination of thought that developed in the previous century. In this, they followed the traditions of Gottlob Frege, David Hilbert, and others in the field of mathematical logic.[93]

The foundations cracked in 1930 and 1931, when Kurt Gödel wrote a series of papers that demonstrated some statements in mathematics could not be proved.[94–96] He constructed a sentence based on the rules of arithmetic that could be proved only if it was wrong. Using the tenets of number theory, the part of mathematics concerned with the addition and multiplication of numbers, Gödel showed that this essential core of mathematics, basic arithmetic, was either self-contradictory or there were things within it that simply could not be proved. He then extended these findings by showing that the problem could be solved only by borrowing from another theory based on stronger, and thus less reliable, assumptions.[97] Gödel shattered the dreams of generations of mathematicians.

Gödel's methods drew on a new field of mathematics concerned with iterative processes. Mathematics after Gödel attempted to synthesize what he had cast asunder. Ulam, von Neumann, and countless others worked to bring coherence to information theory and related fields. The computer was a natural partner, and became an integral part of such research. This field of mathematics resonated in harmony with another, seemingly unrelated, field—molecular biology.

DNA passed through countless generations of organisms since the beginning of life on earth. Perhaps DNA became the keeper of inherited information only after RNA or some other molecule. DNA emerged as the dominant, if not exclusive, mediator of inheritance. Gregory Chaitin from IBM's Thomas J. Watson Research Center closed his book *Algorithmic Information Theory* with observations that clothed Darwin's conclusion in the garb of modern mathematics:

> I would like to end with a few speculations on the deep problem of the origin of biological complexity, the question of why living organisms are so complicated, and in what sense we can understand them, i.e., how do biological "laws" compare with the laws of physics? . . . Biological evolution is the nearest thing to an infinite computation in the limit that we will ever see: it is a computation with molecular components that has proceeded for [a billion] years in parallel over the entire surface of the earth. . . .[98]

Exploring the structure of DNA was more than a practical matter; it was science aimed at the informational core of life. As genome researchers revealed that information, they were not only discovering genes that caused disease,

they were also generating data to contend with the core hard questions facing all of science.

The revolution that took place in mathematics after Gödel and the parallel revolution in physics that replaced the mechanics of Newton with the probabilistic physics of quantum mechanics presaged the future of biology. Simplistic reductionism had to give way to a richer, if less predictive, science. The simple model of a broken gene causing Huntington's disease in a one-to-one correspondence would have to be embellished and adapted to the complexities of the human organism. Most genetic contributions to disease were not so simple. The causal theory had a kernel of truth, but disorders such as Huntington's were the unusual simple case, and even here the biology confounded simplicity. Even that prototype genetic disease showed diverse symptoms, and the age of onset could be determined by genetic "imprinting" (subtle changes in inheritance when chromosomes were inherited from the father rather than the mother). Most other diseases were far more complex.

The information from the genome project would accumulate most rapidly for human disease genes, and for organisms useful in studying human disease, because that is how humans would deploy their resources. Even at this first level, genetic diversity was impressive. As samples were compared from variant human populations, the richness of biology would inevitably come to the fore. With comparison to other organisms, the variety would become overwhelming. Approaching biology from the genome was destined to become a central strategy in penetrating the maze. The unifying force was evolutionary history; the core strategy was comparison of sequences. Shared genetic structure implied similar function.

In writing the biography of great men and women, printing the DNA sequence of their genome would not be a good place to start. Studying the structure of DNA could not explain how Beethoven created his music or how Einstein thought about physics. Genetics offered only a new tool with which to approach the problems confronting medicine and biology—for example, it might shed light on the gene responsible for Alzheimer's disease in the Ross family, perhaps eventually helping to relieve that part of their suffering. At the root of these discoveries, one would find computers running programs based on the work of mathematicians, comparing DNA sequences.

19

DNA Goes to Court

COMPUTER HACKERS were not the only infiltrators in the gene wars. Another, more virulent pest, the lawyer, also began to infest molecular biology. DNA and the technologies to manipulate and analyze it became new frontiers for patent and copyright law. DNA methods were also used to link suspects to crime, mainly rape and murder, thus drawing the pristine science of genetics into the courtroom battles between prosecutors and defense attorneys. Adapting genetics to social functions through law required accommodation on both sides.

In November 1983, residents of Leicester County, England, found the dead body of fifteen-year-old Lynda Mann by a path. She had been raped and killed by an unknown assailant. Traditional forensic methods were used, but the case was still not solved when fifteen-year-old Dawn Ashworth, from a nearby town, was also found raped and murdered in late July 1986. Richard Buckland, a worker at a local psychiatric facility, was arrested. The police attempted to link Buckland to the victims, and contacted geneticist Alec Jeffreys of Leicester University.

Jeffreys was a world figure in the development and analysis of human genetic markers. He was interested by the request and agreed to help out. He used DNA typing on material from vaginal swabs of the victims and compared them to suspect Buckland's DNA. Jeffreys concluded that the two young women had indeed been raped by the same man, but it was not Buckland. Buckland was released, despite having made a dramatic confession. Buckland became the first person exonerated by DNA testing.[1]

The police then began a "genetic sweep" of the population in January 1987, intending to determine the DNA type of all young males in the vicinity. Colin Pitchfork was scared. He resorted to subterfuge, enticing a coworker to substitute for him when blood samples were drawn, so Pitchfork's DNA was not typed. By May, more than 3,600 DNA typings had been performed, but there was still no match to samples taken from the victims. In August 1987, a coworker admitted having substituted for Pitchfork, and six weeks later the police were notified. Pitchfork confessed to both murders and was convicted.

DNA typing had earlier been used to establish relatedness among individ-

uals (to resolve disputed paternity, to enforce child support, or to allow immigration into the United Kingdom), but the Leicester County case was more widely publicized and promised far broader application to forensic testing. The Leicester case inaugurated a new technology for identifying individuals in criminal proceedings and touched off a battle that raged for several years. By the end of 1989, DNA typing had been used in at least eighty-five cases in thirty-eight states in the United States alone,[2] and in spring 1991, every state had used forensic DNA testing.[3]

For prosecutors, DNA typing was especially effective in rape and murder cases. DNA typing might enable them to link criminals to the scene of the crime as reliably as standard fingerprinting, but without requiring that the criminal leave a good fingerprint. In most crimes, there was a struggle, with bloodstains to be analyzed, semen from a rapist, or hair or skin tissue inadvertently left behind. If the perpetrator did leave behind a bit of hair, blood, semen, saliva, urine, or other tissues that could be typed by DNA analysis, then they could be identified. For defense lawyers, DNA typing could be an overwhelming exculpatory technology if there was no match. As in the Leicester case, DNA typing was more convincing than a false confession.

The power of the technology came from linking a person to the scene, not proving that the defendant committed a crime. (In rape, for example, a match between suspect and semen type indicated that intercourse took place, but not that it took place against the victim's will.) DNA typing was clearly a powerful new tool for law enforcement, but important questions remained about how to use it properly.

The techniques were quite similar to those used in pedigree studies for genetic linkage, and indeed used many of the same reagents. There were major differences, however, that emerged as more cases appeared in court. In genetic linkage, a genetic marker is followed through a family. The value of a marker is that it enables one to trace inheritance from one generation to another, to discern which marker was inherited from the mother and which from the father for each member of a pedigree. Typically, in pedigree research, fresh blood samples are taken from those in the pedigree.

In forensic investigations, however, there is less information to start with, since there are no family ties to help interpret the DNA findings. The critical question to answer is: How likely is it that these tissues—such as blood, hair, or semen—came from this particular suspect? The amount of material may be quite small, the sample is unlikely to be fresh, and it may be mixed with tissue from other individuals, as in cases of multiple rape, or mixed samples of both perpetrator and victim. Blood samples are often dried, and the DNA may be partially degraded. Sample DNA may be completely used up in the analysis, precluding reanalysis if the test fails and eliminating the possibility of further tests if initial tests are not definitive. Tests must be performed adequately by the laboratory, so that samples are not switched and criteria for calling a match are reliable.

Most important, however, one is not merely comparing DNA type between parent and child within a pedigree, but rather trying to assess the likelihood that it comes from a particular person, the suspect. That assessment, in turn, depends on how often that DNA typing pattern occurs in the entire population, not just in a family pedigree. The probability of a match thus depends on statistical analysis of DNA typing patterns across the population and knowledge of how prevalent a given DNA type is. The statistical power of DNA typing thus ultimately rests on data that are expensive to collect, requiring systematic survey of the population with DNA typing of very large numbers of individuals.

As DNA typing entered the courtroom, questions about how adequately it had been performed and interpreted began to arise. The process of introducing the new evidence hinged on satisfying the *Frye* standard, a set of legal criteria that grew out of a 1923 murder case. A court was faced with deciding whether to admit evidence taken from one James Alfonso Frye, a young African-American accused of having murdered a white man in Washington, D.C. The prosecution proposed to introduce into evidence data about how his blood pressure responded to questions about the crime, as a measure of his veracity in a primitive precursor of the polygraph test. The court agonized, but ultimately rejected the proffered evidence, noting:

> Just when a scientific principle or discovery crosses the line between experimental and demonstrable stages is difficult to define. . . . while courts will go a long way in admitting expert testimony deduced from well-recognized scientific principle or discovery, the thing from which the deduction is made must be sufficiently established to have gained general acceptance in the particular field in which it belongs.[4]

The court thus established a two-tiered sociological standard for the acceptance of scientific evidence. A court must decide the field whence it arose, i.e., identify a scientific community, and must determine that it was accepted within that community. These criteria were bulwarks against admitting evidence from new scientific techniques until the Supreme Court cast down the Frye standard in 1993. The reason for special caution was a belief that scientific data might unduly sway judges and juries. The *Frye* criteria, however, were rather vague. Just how to define a field and how to assess consensus was far from clear. The alternative to the *Frye* standard, under federal rules of evidence, was premised on relevance to the matter at hand—admitting into evidence anything that helped the court to assess the facts. The federal rules were developed under precepts outlined in a 1975 statute and subsequent amendments.[5] Here also, while not so rigid as the *Frye* criteria, the judgment of admissibility turned on whether expert testimony would be useful in ascertaining or understanding the facts and required a judgment of the qualifications of experts. Rule 702 specified that expert status could be inferred from "knowledge, skill, experience, training, or education."

In the United States, most early DNA typing was performed by two private

firms. One, GenMark, was affiliated with the British chemical giant ICI, and licensed the methods developed by Alec Jeffreys. Lifecodes was a small, independent firm based in Valhalla, New York. These private firms initiated forensic typing on a fee-for-service basis for prosecutors or defense attorneys.

DNA tests were first brought into American courts in 1986, but really caught hold in 1988. The Federal Bureau of Investigation began to focus on the promise of DNA testing as the technology was introduced into courtrooms throughout the states. The FBI set up a laboratory in Quantico, Virginia, to perform tests on request and to train those who wished to learn about the technology from state crime laboratories. The FBI also proposed to standardize the methods used so that results could be compared from one state to another and DNA typing profiles could be matched at the federal level, comparing samples analyzed by laboratories in different states. A California investigation might turn up a match to a Colorado serial killer, for example, using only the limited data from a computer code for DNA typing. The FBI could then notify police in both states to contact one another to pool their evidence.

As work on the OTA report on the genome project was winding down early in 1988, the number of criminal cases using DNA forensics rose quickly. It became clear that an assessment of forensic typing could also be useful. OTA thus began an assessment that produced a separate report in July 1990.[2] The National Research Council of the National Academy of Sciences also formed a committee to assess forensic uses of DNA. The committee, chaired by Victor McKusick, began work in January 1990 and released its report in April 1992.[6]

DNA evidence was first accepted as evidence in *Florida* v. *Andrews*;[7] Tommy Lee Andrews was accused of having raped and slashed several women. DNA typing was used by the prosecution, and he was convicted in November 1987. In October 1988, the Florida State Court of Appeals for the Fifth District upheld the admission of DNA typing evidence.[2] The prospects for DNA forensics looked rosy, but then some sloppy work showed how it could be troublesome.

The watershed case that cast doubt on how well DNA forensic testing was being performed was the highly publicized *New York* v. *Castro*. This case was tried in the same court caricatured in Tom Wolfe's novel *Bonfire of the Vanities*.[8] Lifecodes had performed the DNA typing, concluding that a bloodstain on Jose Castro's watchband matched the blood types of a woman and daughter murdered in the building where he was a janitor. Lifecodes claimed that the likelihood of the match they found was one in 738 trillion.[9] When expert witnesses scrutinized the evidence, it turned out that Lifecodes had ignored two bands in the DNA typing pattern, had failed to run appropriate controls, and had not applied its own quantitative criteria for matches.[7,9] Lifecodes had thus interpreted its evidence in what could be charitably be called a creative fashion. These lapses called into question the entire enterprise of DNA forensics.

The expert witnesses called by both prosecution and defense took the

unusual step of going outside the courtroom to confer among themselves, and they prepared a report for the judge. The judge ruled that the evidence could be introduced to exculpate the suspect, but not to corroborate his guilt. The court clearly indicated that DNA testing was, in theory, admissible as evidence to identify the suspect positively, but doubts about laboratory procedure and interpretation in the current case made it inadmissible for that purpose. Castro pled guilty, and while the status of DNA testing in the case was thus not crucial to its outcome, the exposure of some pitfalls in DNA forensics became a lasting residue.

In other cases, Lifecodes presented statistics suggesting that the chances of a match were one in several hundred million or in the billions. The claims were outrageous given the paucity of the population-genetic database, which was held as a proprietary secret. Beyond the insufficiency of the population genetic data, there was always a possibility that the laboratory inadvertently switched samples, or that the person had a twin and did not know it (DNA typing, unlike standard fingerprinting, could *not* distinguish identical twins). The likelihood of such errors was obviously much higher than the figures being quoted in court. The *Castro* case ushered in a debate about laboratory practices, consistent band-matching criteria, and standards for interpreting the statistics.

The courtroom conflict between prosecution and defense began to spill over into the scientific community. A relatively small number of human geneticists, particularly those who were knowledgeable about both DNA typing and population genetics, were called as expert witnesses in many cases, but they did not agree among themselves about how to interpret the tests. The center of the controversy was the degree and significance of population substructure.

If the accused person came from a population that often had a DNA-type profile unusual in other groups, and if this group had few or no members in the population database used for interpretation, then the result could be highly misleading. Suppose, for example, that the suspect was a Basque and that Basques had type Z very frequently but other groups did not. There might be hundreds of thousands of Basques with that type. The database would not reveal this fact because it would include few Basques and would lump them with Caucasians. In the total database, the Basque pattern would appear quite rare. Moreover, Basques might be expected to cluster in the same neighborhoods, say the one where a murder or rape took place. If DNA types did indeed vary among subpopulations, errant statistics could make it seem that a match was far more significant than it actually was. Another possible source of errant interpretation was if two traits were assumed to be independent, but were actually associated with each other. Nordics, for example, might often have blond hair and blue eyes, but if the probabilities of blue eyes and blond hair, both uncommon traits, were multiplied together, it would seem extremely unusual for individuals to have this combination. There were few data

to assess how often this kind of bias was present for the new DNA markers, and so there was ample room for divisive scientific combat.

The scientific controversy spilled onto the pages of *Science*. Two groups of highly competent population geneticists took opposite sides on this question. One article cast doubt on how forensic tests were being employed and asserted a need for considerably more data about the frequency of DNA types among disparate populations before the technique should be used to decide the fates of the accused.[10] A companion piece, commissioned by editor Daniel Koshland, doubted that population substructure was large enough to mislead juries and judges.[11]

Those interpreting DNA forensics typically used different base statistics, depending on the race of the suspect. This practice was troubling from both social and technical points of view. It was inherently disturbing to use race overtly in criminal proceedings. Moreover, the "racial" categories corresponded only poorly to population-genetic knowledge. The Federal Bureau of Investigation used a category of "Hispanic," for example, but this could refer to a person from a Caribbean island, someone from Aztec, Inca, or Mayan extraction, or someone whose ancestors came from Spain and Portugal—a hopeless mishmash.

The task of sorting out the technical arcana fell to the NRC committee. The NRC report was caught in a crossfire between the FBI and prosecutors on one side and defense attorneys on the other. The battle was joined by geneticists. The intensely adversarial ethos of the courtroom seared the professional egos of many, as their motives were impuegned, inconsistencies amplified, and characters flayed not only before the jury but also in the public media.[12] A network of prosecutors and a countervailing network of defense lawyers resorted to tactics of intimidation and persistent annoyance vastly more aggressive and personal than the usual intellectual fencing within science. Some scientists, although not the most prominent scientific authorities, and not a few lawyers made a living on the introduction of DNA forensics. Most of the fights centered on how to interpret laboratory results.

The 1990 OTA report called for quality control measures and noted the controversies surrounding interpretation of population genetic data.[2] The NRC committee attempted to formulate standards for interpretation, to forge a consensus about how best to use DNA test results in court. As the report approached release, the *New York Times* broke a story that concluded the report would recommend a moratorium on DNA forensics until there were better standards.[13] This forced the committee to schedule a press conference in great haste, to dispel the call for a moratorium recounted in the story.[14]

The NRC report made a series of significant recommendations. It called for an independent expert body, outside the FBI, to monitor laboratory practices and to make recommendations on how DNA forensic testing should be performed. The committee's most significant contributions but also its greatest vulnerability, came from recommendations about how to handle the pop-

ulation-genetic analysis. The committee reviewed evidence that population substructure was probably not a major source of errant matches, but it allowed that "population substructure may exist." It acknowledged that existing statistical databases were insufficient to determine the extent of population substructure, and argued that "the solution, however, is not to bar DNA evidence, but to ensure that estimates of the probability that a match between a person's DNA and evidence DNA could occur by chance are appropriately conservative."[6] The databases should be made better, and this could be done by directly measuring the extent of population substructure among ethnic groups.

The controversy over DNA forensics thus reinforced the need for better data about human population genetics. This had already been raised as an urgent priority among anthropologists and paleontologists who hope to use genetics to understand human origins and historical migratory patterns. The need for robust forensic databases gave the same data a decidedly practical twist, with lives hanging in the balance. Controversies about how best to interpret population-genetic data that had long been obscure and of only academic interest were suddenly directly relevant to the fates of suspected criminals, and to the pursuit of justice. Whether data would dispel the factiousness of the population-genetics community was open to doubt, but if not, there was a long future for careers in expert testimony. The first step, and the best hope, was to collect empirical data on human populations by going out and sampling them.

A recommendation to stop using race-specific analyses was also a major advance. The committee suggested that the frequency of any given DNA marker pattern should be interpreted to the benefit of the suspect, under a "ceiling principle." The number used to assess the likelihood of a match should be taken from the population group with the highest frequency. This default assumption was a clever way to get around the troublesome process of determining racial origin. Instead of trying to decide which "race" the suspect came from and applying different statistics for each group, the suspect's racial background would be irrelevant, and the suspect would be given the benefit of the doubt for each marker tested. If prosecutors needed more statistical power, they could order more markers to be tested, possible in many but not all cases. This proposal would bring down the probabilities from the ludicrous range of one in millions or billions, but the technique would still generally be far more reliable than eyewitness identification or blood-protein tests. The committee suggested setting arbitrary conservative probabilities until data began to flow in from the empirical population surveys.

The committee thus cut the Gordian knot, hoping to preserve the admissibility of the evidence, to shore up the regulatory framework, and yet to interpret the evidence in a conservative and scientifically defensible manner. It was not clear, however, how judges would react. In what was purportedly a review of books about the genome project but proved more a platform to air his views, Harvard geneticist Richard Lewontin noted that the NRC report

might not resolve the population-genetic controversy. Judges might focus on the report's ambiguity, calling for empirical data, rather than accept the committee's interim solution of ceilings and arbitrary marker frequencies.[15] A cautious response would favor waiting for more data about the markers being used in specific populations. The courts predictably differed in how tightly they embraced DNA forensics. Some accepted DNA forensic evidence, while others awaited resolution of the population genetic issues.[16] While the eventual acceptance of DNA forensics was not in doubt, the speed with which it would become routine was highly uncertain and appeared likely to differ markedly among jurisdictions.

The controversy refused to die, and even as some courts began to admit DNA forensic evidence more readily, another controversy broke out in *Science* with the publication of an article critical of the NRC report and a news feature on the same topic.[17;18] This time, the NRC committee was lambasted for erring too far on the side of conservatism. A group of population geneticists cast doubt on the significance of population substructure for those markers being used in forensic work. They disagreed with the logic behind the ceiling principle and asserted that most data suggested that marker frequencies could generally be multiplied together—the procedure that produced such astoundingly large odds ratios. They pointed out the need for much larger samples of population groups than those suggested in the NRC report to get sufficient data; a survey of the proposed size would generate relatively unreliable and unduly high estimates of marker frequency because the number of individuals sampled would be low and the margin of error correspondingly high. The upshot was that courts were being misled into a too conservative stance on DNA forensics by the NRC committee, and that the empirical surveys intended to solidify the basis for interpretation would not be sufficiently robust to restore balance. The NRC report was thus being attacked from both sides. Some critics claimed it was unduly conservative, while others contended the NRC committee had too readily accepted DNA forensics. The NRC commenced a second DNA forensic study in the summer of 1993, hoping to finally quell the controversy.

The courtroom entry of a new genetic technique, derived from gene mapping efforts, was noisy and slow. The problems emerged only as specific cases provoked scrutiny of existing practices. Abstruse questions of population genetics, a mathematically complex and relatively small academic subspecialty, were suddenly exposed to the harsh realities of the criminal justice system. Science collided with an adversarial court tradition, and the result was five years of turmoil, entailing hundreds of hearings, thousands of hours, and millions of dollars. In the wisdom of hindsight, the sources of controversy could have been resolved by empirical research, standardization of methods, and conservative race-neutral interpretation. But like the field from which it arose, DNA forensic testing took a bumpier road to acceptance. Yet it was not

the only area where science and law collided. There was also the matter of who owned the genetic terrain now being explored.

New relationships between industry and academia proliferated in molecular biology soon after the invention of gene splicing in the mid-1970s. Molecular cloning and fusing of cells bred commercial biotechnology.[19;20] The commercialization of molecular biology coincided with a shift in government policies to promote U.S. economic competitiveness. Values within biomedical research groups in universities shifted from suspicion of commercial attachments to active promotion of technological spinoff.

Industry began to fund more biomedical research, particularly work related to development of new drugs. Government funding grew, but at a pace well behind that of pharmaceutical firms, which significantly increased their research and development efforts as a competitive strategy. In the mid-1980s, private funding for biomedical research and development surpassed NIH's; by the end of the decade, it was greater than federal funding from NIH and all other agencies combined.[21] Catching hold of the best in new science became an important element in drug discovery, driving pharmaceutical firms to heavy research investments as a matter of financial survival.[22]

Changing intellectual property law was a prominent feature of this policy turnabout—the new age of molecular genetics came in with a patent. When Herbert Boyer and Stanley Cohen patented their method for splicing DNA in 1976,[23] it caused quite a stir. In 1980, the U.S. Supreme Court ruled that a microorganism, a living thing, could be patented in *Diamond* v. *Chakrabarty*.[24] The trend to promote commercial applications of biomedical research continued under a series of new public laws and executive orders throughout the 1980s. These consistently encouraged patents by U.S. institutions receiving federal grants and contracts, by conferring substantially greater authority to those receiving federal funds.[25] Congress was presented with evidence that when the government owned patent rights, it did not foster commercial applications. Several studies suggested that the government was not aggressive in pursuing patents and did not license them or otherwise ensure their translation into useful products. It seemed reasonable to assume that if those doing the research had a stake in patents, they would pursue commercial gain more assiduously.

The statutory changes began with the Patent and Trademarks Amendments of 1980[26] and continued in the Trademark Clarification Act of 1984[27] and the Technology Transfer Act of 1986.[28] President Reagan issued Executive Order 12591 in April 1987 to promote technology transfer out of federal laboratories. Congress and the President sent strong signals that they wanted the investment in science to pay off in the form of patents held by institutions of all types that received taxpayers' research dollars. Universities were expected to license their patents to commercial firms, thus harnessing biomedical re-

search to commercial enterprise. American firms were given patent rights in most cases, and foreign firms and research institutions were given incentives to involve US manufacturers. Just how to transform biomedical research mavericks into team horses, however, was a more complex matter.

Intellectual property law would be at least part of the rigging, but in biotechnology, intellectual property was in a tangle. As universities and small dedicated biotechnology companies developed new techniques and new products, the scientific races for priority spilled over into battles to secure patent rights, with different rules in the United States and other countries.[29;30] The number of biotechnology patent applications reached 6,900 in January 1988.[31;32] The Patent and Trademark Office (PTO) in the Department of Commerce disposed of 2,200 biotechnology patent applications in 1987, but received over 3,100 new ones that same year.[31] The PTO was deluged with applications, and it staggered under the burden.[33] In 1988, the PTO created a new unit to handle biotechnology patents in response to the growing demand.[31] Universities and companies continued to complain about the patent process nonetheless: the flow was too slow, the level of expertise of patent examiners insufficient to mete out the rewards of innovation, staff turnover was too high, and the decisions of the office unreliable and thus inclined to exacerbate rather than abate the surge of costly patent litigation.[34]

Approval of a patent application was just the start. If there was enough money at stake, residual uncertainties would later surface in suits about who was infringing whose patent, to be decided case by case, in years of costly litigation. Patent rights regarding therapeutic pharmaceuticals, many of them based on patented human genes, were disputed in many hard-fought legal battles. These were of great consequence to biotechnology in general but only tangentially related to the genome project. Some patent uncertainties, however, arose in matters directly connected to genome research. The technique of mapping with RFLPs was itself the subject of a patent application filed in the early 1980s, first by a Utah group and then pursued by Stanford University. The polymerase chain reaction was the battleground for a patent dispute between the chemical company Du Pont and the biotechnology firm Cetus, recounted in Chapter 4. By far the greatest area of uncertainty, however, was how the coming flood of DNA sequence information would work its way into the legal framework for deciding how far property rights extended and how well they would protect an inventor.

Uncertainty about patenting gene maps and DNA sequence information was apparent from the early debates about a genome project. The criteria for granting patents and registering copyrights were clear, in principle.[20;35] How to apply the general criteria to new technologies and new scientific strategies for defining biological functions was not, however, immediately obvious. Walter Gilbert was among the shock troops invading this hotly contested legal territory.

When Walter Gilbert embarked on raising funds to start the Genome Corporation in 1987, he claimed he would copyright the information and sell it to companies or researchers who wanted it. They would purchase access to the information because he could generate it more quickly and cheaply than they could themselves. This gesture toward a commercial venture provoked an outcry among molecular biologists. As Lennart Philipson and John Tooze put it, commenting from a European perspective, "the prospect of private capital financing this work and then keeping secret the sequence information and restricting access to the libraries of clones from which it was obtained, in order to generate corporate profits, is too obscene to find many supporters."[36] Gilbert replied that biologists had also complained about buying restriction enzymes and laboratory glassware when they were first produced commercially.[37]

The 1988 OTA genome report waded into the morass of intellectual property law and surveyed the noisome debate about how it would apply to genome studies. Susan Rosenfeld, a lawyer from New York, prepared a background paper,[25] and OTA convened a workshop in June 1987.[38] *Science* summarized the meeting, asking "Who Owns the Human Genome?"[39] Those around the table agreed that one could not patent sequences *per se,* and while Gilbert's idea of a copyright seemed plausible, those assembled cast doubt on whether copyright protection was sufficient to protect a massive private investment.

Irving Kayton argued in 1982 that clones and sequences could be copyrighted, like computer programs or photographs.[40] Susan Rosenfeld argued this was unlikely to prove true in fact, and even if a database could be copyrighted, the subsequent uses to which the data were put could not be controlled. A later OTA report cited unofficial statements from the Register of Copyrights and the Copyright Royalty Tribunal that DNA molecules or sequences would not be protected under copyright in the same way as art, literature, computer programs, or electronic media.[35] The 1987 workshop surveyed disagreements about other intellectual considerations related to genome research without reaching any conclusions. Various legal experts held different opinions about whether scientific data were property[41] and about the degree to which trade secrets would be effective in biotechnology.[42;43]

The matter of intellectual property law was raised time and again at genome conferences. At DNA sequencing conferences, there was debate about just what information needed to be kept secret before filing a patent application. At ethics conferences, there was concern about balancing the advantages of intellectual property protection against the need to pool information expeditiously, to reduce duplication, and to broaden access to important data. As George Cahill from the Howard Hughes Medical Institute put it, "What is the bucks-to-ethics ratio here?"[38;39]While the 1987 workshop raised questions about whether DNA sequences could be patented in general, as part of a general mapping of the genome, it was equally clear that genes that were isolated and manipulated could indeed be patented. Rebecca Eisenberg, from

the University of Michigan Law School, analyzed the question of just what could be patented in a 1990 law review article.[44] She argued that the critical criterion was "whether the claimed invention is the result of human intervention," adding that "if the DNA sequence is identical to a sequence that exists in nature, it may still [be patented] if the patent applicant has made the sequence available in an isolated or purified form that does not exist in nature." Many genes had been found and sequenced, and case law upheld the patent claims for new drugs based on those genes.

Eisenberg noted a potential conflict:

> . . . The patent system rests on the premise that scientific progress will best be promoted by conferring exclusive rights in new discoveries, while the research scientific community has traditionally proceeded on the opposite assumption that science will advance most rapidly if the community enjoys free access to prior discoveries."[44]

Eisenberg then sketched out the possibilities of defining research uses exempt from patent protection, permitting research to proceed without worry of being sued for infringement. This would preserve the right to use the information for noncommercial purposes, such as constructing genome maps in the public domain, but would preserve the power of patent protection in the commercial realm. Another possible solution was suggested by Dennis Karjala and others who helped prepare an outline of legal issues confronting the genome project.[45] A new form of intellectual property protection might be tailored to biological technologies. This option would attempt to retain the incentive for private research investments while acknowledging the intuitive disharmony between the notion of an "invention," with its image of a machine to be protected by a traditional patent, and the newfound commercial power of biology.

Despite continued debate, the issue failed to provoke a policy response until it came up at a Senate meeting in July 1991. Matthew Murray, who helped arrange a previous 1990 hearing on the genome project for Senator Pete Domenici, returned to Capitol Hill for a short stint to set up a progress review meeting on the genome project, a senatorial "annual checkup." Domenici's main interest remained commercial spinoff of genome research.

The review of scientific results was upbeat. The chromosomal defect underlying the fragile X syndrome, a common cause of mental retardation mainly affecting males, had recently been uncovered, and Baylor University geneticist Tom Caskey was present to tell the story, as one of the stalwarts in a massive international collaboration. The discovery had used the methods promoted by the genome program and had involved several laboratories supported by genome project monies.[46]

Domenici's meeting sparked an exchange about how and when to file patent applications on findings from large-scale sequencing projects. John Barton from Stanford Law School pointed out that while the general patent criteria were generally accepted, their interpretation in the specific case of

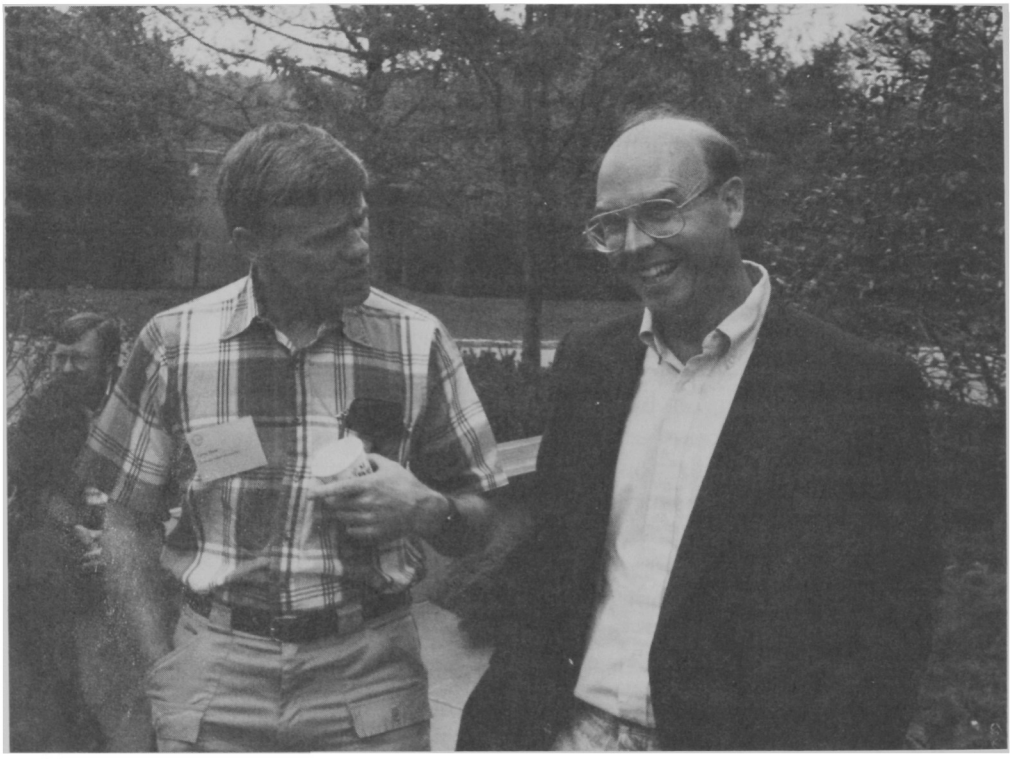
finding genes through sequencing was a gray area. At the root of the uncertainties was the new scientific process of discovering DNA sequences before knowing their function. It seemed intuitively clear that sequences, like mountains, could only be discovered, not patented. Yet it was equally clear that patents already protected the isolation and purification of genes and development of protein products encoded by them. The patents rested on a legal distinction between discovering a gene and producing it in a new and useful form, which constituted the invention. DNA sequence information could be the initial step in a long journey leading to diagnostic tests and might even might lead to new treatments in some cases. The open questions were how and to what extent DNA itself would be a patentable subject matter.

NIH scientist J. Craig Venter announced at the Domenici meeting that he had been isolating DNA fragments from brain tissue, corresponding to stretches that coded for proteins, and that NIH filed a June 1991 patent application to cover the sequences. Venter's group was collecting such fragments, isolating them, and determining short stretches of DNA sequence as gene indices. In consultation with the NIH Office of Technology Transfer, NIH filed patent applications on several hundred of them, listing Craig Venter and his coworker Mark Adams as the inventors.

Most of us in the room were startled by the disclosure. Watson was aware of the patent application, but did not support it. Adler and Venter had conferred with Robert Strausberg in the genome office as they frenetically helped prepare the patent application, but within the genome office, there was considerable doubt that the sequences were patentable. Adler and several lawyers with whom he worked, however, thought that the sequences were very likely patentable. From their perspective, NIH ran a serious risk if it failed to patent the gene sequences. If another group later succeeded in securing similar patents, NIH would certainly be criticized. Congress would surely excoriate NIH if, for example, a Japanese firm grabbed the patent rights for genes, when NIH might have been able to confer a preference for American manufacture through licensing its patent rights. Moreover, failure to patent might also make it difficult to patent full genes when they were found. If NIH's data were published without patents and scientific groups later isolated the genes in a more useful form, the prior publication of NIH data might make the subsequent gene purification seem obvious, and thus unpatentable. If no patent application was filed, NIH would irreversibly foreclose its future options.

Venter worked as an intramural scientist in the National Institute for Neurological Disorders and Stroke (NINDS). NINDS was bureaucratically separate from, but scientifically linked to the NIH genome center. When Venter mentioned his patent application at the Domenici meeting, Watson was lying in wait and took aim with heavy artillery. Watson asserted that it was sheer lunacy to patent such incomplete information. He objected strenuously that the automated sequencing machines "could be run by monkeys," and if sequences could be "locked up" by the first person to sequence

a part of a gene, without knowing its function or even the sequence of a significant fraction of a gene, biomedical research could be tied up in knots by patent litigation. The exchange initiated a running battle that culminated in Watson's resignation nine months later. After the meeting, Watson mentioned privately that he had "been too hard on Craig," and that Venter was only following the advice of others at NIH, but he did not back down from his stance that the patenting idea was fundamentally wrongheaded.



J. Craig Venter and Leroy Hood were instrumental in devising methods to automate the sequencing of DNA. Venter's work on a system for rapid DNA sequencing, originally done at the National Institutes of Health, led to a controversial patent application that pitted NIH against a formidable array of opponents. Hood, who initially headed a major research group at the California Institute of Technology, is now at the University of Washington. *Courtesy Institute for Genomic Research*

The conflict grew from small beginnings, intimately intertwined in the early history of large-scale DNA sequencing efforts. Venter ran one of the largest sequencing laboratories in the world. His work centered on understanding genes for molecules involved in transmitting signals between nerve cells—enzymes that made neurotransmitters and receptors for intercellular communication. This work drew him into sequencing the genes encoding the

proteins. He made a commitment to DNA sequencing as a major scientific strategy to understand the process of neural communication, several years before this approach became generally accepted. Venter believed in the technology. He organized the first international DNA sequencing conferences, which became annual events, and also helped plan an early international meeting on ethical aspects of genome research, which took place in Valencia, Spain (the second Valencia meeting, in November 1990).

On the technology front, Venter's laboratory had a cooperative research and development agreement with the California instrumentation company Applied Biosystems. His laboratory secured early access to instruments in development, including state-of-the-art DNA sequencers, and his laboratory group was a proving ground to help the company work out technological kinks. While Venter had stable research funding through the National Institute on Neurological Disorders and Stroke, he applied for funding from the National Center for Human Genome Research. After discussing the possibilities for almost a year, Venter agreed to send in a proposal to be considered for funding. Watson initially asked him to submit a brief description, but the rules changed when the genome center decided that Venter's intramural funding request should be considered by the same peer review group considering university applications for large-scale sequencing. Several projects proposals had been submitted in late 1989 and early 1990. Venter initially proposed to sequence the terminal stretch of the X chromosome. It was an audacious proposal to mount an assault on a region known to contain a relatively dense cluster of at least thirty disease-associated genes.

The review of sequencing grants took place as acceptance of automated sequencing instruments was rapidly shifting. Some scientists were simply convinced that the current generation of machines would never prove useful for large-scale sequencing. Venter's laboratory had begun to turn out solid data with greater reliability and at a faster rate than perhaps any other group in the world using the Applied Biosystems instruments, but the early record of difficulty in getting automated sequencers to work reliably had tarnished their reputations. Some had taken to calling the machines "$100,000 paperweights."[47] Unlike the other investigators rejected in the first review, Venter's group never secured genome project funding. The reasons were complex, and partially due to Venter's changing scientific direction. A growing frustration with delays in getting funding from the genome center also contributed to the decision.

Venter's X chromosome sequencing proposal had evolved from earlier discussions, and would continue to evolve. Venter already managed a large and growing research team without genome project monies, as he had direct funding from a separate NIH institute. He did, however, want genome funds to expand the scale of his work. Watson was initially quite enthusiastic, and said he would devote $5 million to Venter's work. The politics of sequencing, however, were intense, as there was considerable opposition to large-scale

sequencing among molecular biologists, even for model organisms such as yeast, nematodes, and fruit flies. The opposition was even stiffer when it came to sequencing human DNA, which had a lower density of genes, a far less elaborate genetic map, a greater depth of ignorance about gene location and function, and less powerful genetic tools for analysis. There was also considerable disagreement about the proper sequencing method (whether it should be done by hand or by automated sequencers) and the proper strategy (whether it should start from unedited chromosomal DNA—genomic sequencing—or only from those edited sections known to code for protein). The fierce opposition forced Watson to retrench on his initial commitment.

Venter worked directly at NIH, and so Watson could have directly funded the work with an internal review of its merit. Sensitive to opposition within the biomedical research community, the NIH genome center decided on a cautious approach, and Venter's project was put on hold along with other major sequencing proposals, while the policy was sorted out. NIH and DOE appointed a joint working group on DNA sequencing that met in July and September and recommended a special "request for applications," soliciting grants to do large-scale sequencing, and specifying minimum criteria to meet in those applications. Watson had initially asked Venter to submit a short summary of his ideas, but Venter was now asked to submit a more formal application to be judged with others from outside NIH.

The process entailed a special request for applications and a review process, causing another six to eight months' delay in a discussion that had been going on for over a year. In the review, Venter's group was the only one from an NIH-based intramural group. Having an intramural proposal reviewed by much the same group considering grant applications from outside NIH was an unusual move. Venter's group alone held a face-to-face meeting with the study section—the scientific review panel charged with assessing the scientific soundness of the proposals. It was a difficult meeting, and the study section assigned the proposal, along with most others, a priority below that needed to obtain funding. Walter Gilbert's proposal to sequence a bacterial genome and Leroy Hood's proposal to sequence large stretches of DNA containing genes for immune function also had a rough ride, although they were eventually funded in later funding cycles. While Venter's review was relatively unfavorable, the genome office nonetheless told Venter he, like others, was likely to be funded if he revised his approach in light of the reviewer's comments. Venter began to formulate a proposal to continue ongoing work on several different chromosomal regions—those known to contain the genes for Huntington's disease (chromosome 4), a part of chromosome 19, and regions linked to disorders on chromosomes 17 and 15.

The new strategy was settled between Watson and Venter at a meeting on Hilton Head Island, South Carolina, at Venter's 1990 DNA sequencing meeting. The first day of the conference coincided with the date that Watson had chosen as the official start date for the genome project, October 1, 1990.[48]

Before this proposal was fully evaluated, however, Venter withdrew his request for funding, in an April 23, 1991, letter to Watson. In that letter, Venter noted:

> Had we started over two years ago, when we first discussed automated sequencing, we probably would have completed 1-2 megabases of contiguous sequence by now. This has represented another major frustration for me. I am concerned that the bureaucracy that is a necessary part of the grant review process cannot keep pace with the rapid developments in the genome area.[49]

The letter also laid out his scientific reasons for wanting to take a different scientific tack, focusing on coding regions rather than genomic sequencing of unedited DNA from human chromosomes. Venter decided to pursue a line that promised to produce results quickly and that would link sequencing to functional clues and gene mapping directly. Venter's change of heart came partly from his frustration with bureaucratic unresponsiveness and partly from a belief that the tedium of direct genomic sequencing yielded data that were too hard to interpret.[50] He argued it would be more efficient to first sequence protein coding regions, which would in any case be essential to interpreting any genomic sequence derived directly from chromosomal DNA. The new strategy dropped the idea of sequencing a stretch of the X chromosome and instead focused on protein-coding throughout the genome.

The idea of focusing on protein-coding regions had been proposed time and again in the genome debate, indeed even before and during the June 1986 contretemps at Cold Spring Harbor Laboratory,[51] but had never become policy at the NIH genome center. Sydney Brenner championed this strategy for the initial genome efforts in the United Kingdom, and it was also pursued by groups in Japan, France, and elsewhere. In the United States, the Department of Energy decided to include a similar component in its genome research program beginning in 1990. Venter was an adviser on this effort, and his laboratory was among those funded by DOE.

Venter's main innovation was the nature of the indexing system for the gene catalog, based on automated sequencing to identify short stretches of DNA. Venter's work on brain molecules made this a natural strategy. Brain cells produced a far wider variety of proteins than any other organ, and so were logical sources from which to start a gene catalog. The global strategy to determine DNA sequences from protein-coding regions was a natural extension of his brain research and required no funds from Watson's genome center. Venter's group published initial results in June 1991[52], the same month they filed the patent.

Starting a sequencing effort from protein-coding regions of DNA was a quick way to identify new genes and begin to index them. It was also an efficient way to find functional clues about newly discovered human genes, by comparing sequence similarity to genes of known function from other organisms.[49;52–55] The index could be created readily, but would be incomplete.

Short sequences from expressed regions could indicate where genes were located on a chromosome map and could be used to fish them out of the genome.

The short sequence "tags" would not, however, be a complete inventory of protein-coding regions. Some genes were difficult to isolate and did not appear in the standard collections that were the starting point for Venter's effort. Moreover, since only a short stretch of each gene's DNA was known, an investigator with only a part of a gene sequence looking for his or her gene could miss a match until the entire gene sequence was logged into the catalog. The catalog would thus be relatively easy to construct, and would be quite useful for identifying candidate genes in a given region, but the information was not archival or comprehensive.

The great advantage of the approach was its speed, its ability to suggest functional clues based on sequence similarity to known genes, and its identification of previously undiscovered genes of unknown function. These unknown genes were truly "Terra Incognita," and the gene catalog could, with a bit more work, include their location on the human chromosomes. As such a map neared completion, a group hunting for a disease gene might simply go to the catalog and look for tagged genes from that region, whether or not the genes' functions were known. A group that managed to link Alzheimer's disease to a chromosomal region, for example, would turn to the gene catalog to find the list of genes in that region. This list would, in turn, enable them to study the DNA sequences from those known genes, hoping to find a mutation correlating with the presence of disease.

Watson did not oppose the concept of work on protein-coding regions, but he wanted to ensure that the overall genome maps, the first goals of the genome project, were completed. The genome office did not fund Venter's work, or other similar proposals from others. Their view was that partial gene sequence catalogs were not substitutes for the global and complete maps that were the goal of the genome project, but rather were useful resources that could later be integrated into more complete databases.The past tensions between Venter and the NIH genome center blossomed into a public conflict. Venter did not regard his effort as a substitute for the genome project, and himself noted that his approach did not "eliminate the need for the Human Genome Project."[56] Venter told *Science,* however, that his approach was "a bargain by comparison to the genome project."[56] His choice of phrases was unfortunate, seeming to offer a contrast rather than a complement to "the genome project." For its part, the genome center did not go out of its way to welcome Venter's effort. Watson never responded to Venter's letter, for example. The damage was done; the knights were off on separate paths in the quest for the Holy Grail.

At the Domenici meeting in July 1991, Venter was personally stung by Watson's attack in front of the senator and the science press. Watson and others at the genome center were irked, in part, because they were not directly

involved in the patent applications. Reid Adler spoke with Robert Strausberg of the genome office as he was preparing the patent application, and there was a formal meeting to discuss its implications a week after it was filed. The decision to file the patent application was made by Venter's group, senior administrators at his institute (the National Institute on Neurological Disorders and Stroke), the Patent Policy Board at NIH, and the NIH Office of Technology Transfer, headed by Adler. The genome office was notified, and did not object, but neither did it endorse the action.

Venter did not initially think about filing a patent application. Adler learned about Venter's work through a letter from Max Hensley, senior patent counsel at the biotechnology firm Genentech, who urged him to talk to Venter about whether he should apply for a patent.[57;58] Adler had never met Venter, but happened to bump into him in the hall when Venter introduced himself to ask for directions. Venter had an article accepted for publication in *Science* just a month or so hence, which meant that NIH would have to move very quickly. To preserve foreign patent rights, NIH would have to file the patent application before the publication date. Having decided the sequences might be patentable, it might be incumbent on NIH to file a patent application to comply with federal law.

Adler argued that "it was worth filing the application if for no other reason than not to miss the boat."[59] He was breaking new ground in intellectual property law; Venter was pursuing a scientific strategy that promised quick payoff. Others were less enthused. The American Society of Human Genetics drafted a policy statement against Venter's patent practices and asked for a preemptive declaration by the Patent and Trademark Office.[60;61] The Human Genome Organization followed suit.[62] The heads of the NIH and DOE advisory committees wrote to NIH director Bernadine Healy asking that the patent applications be made public so they could be openly debated. The committees were "unanimous in deploring the decision to seek such patents."[63]

The nature of what was patentable had been continuously expanding during the 1970s and 1980s, especially in the United States. The general patent criteria were novelty (having made something new), nonobviousness (having done something that would not be readily apparent to those "with ordinary skill in the art"), and utility (having found something that had commercial potential). If the isolated sequences were indeed newly discovered, they would be judged novel. Whether the process was obvious or not depended on the details in the application and a difficult judgment about the state of the field at the time the patent application was filed. Utility claims were even more difficult to predict. The standard in most of the world required a specified commercial prospect. Some countries held a patent valid only for those uses listed in the patent claims. In the United States, however, the scope of utility claims had become progressively more permissive. One generally needed only a reasonable prospect of some use.

Patent criteria might be clearly specified by statute and case law, but applying them to DNA sequences was fraught with uncertainty.[64] The initial NIH patent application in 1991 was very broad, claiming not only the known sequence, but also its gene, the protein produced by the gene, and any antibodies raised against that protein. In a standard patenting tactic, a February 12, 1992, modification (a "continuation in part") added 2,375 sequences to the list claimed and narrowed the claims to the sequence and its corresponding gene.[53; 54]

The process for finding the fragments was taken out of the patent application and separately filed as a statutory invention registration, which was by definition dedicated to the public. Such registration did not secure a monopoly right, but if granted would preclude others from patenting this part of the gene-hunting process. It was a defensive move to preclude others from asserting a monopoly later. The 1992 continuation in part restarted the patent clock and rekindled the public debate.

The issue was not about access to the sequence information or to the DNA being sequenced, although many of the objections to the patent application mistakenly focused on these issues. Venter immediately released his sequence information to GenBank and sent the DNA fragments to a repository once the patents were filed. Making the information public after filing did not endanger the patent.

NIH did make attempts to solicit views on its action. The Office of Technology Transfer held a meeting within weeks of when the patent application was filed, and another public meeting in November 1991. Between the June and November meetings, the patent application had become a major biomedical research policy issue, debated widely in the science press. NIH was vigorously attacked for making a preemptive move that could confound domestic collaboration on the genome project and would complicate international cooperation. A decision that had been made in the emerging routine of technology transfer policy within NIH was thus elevated to the level of the NIH director, Bernadine Healy.

Healy first learned of the patent application in the fall of 1991, when reporters began to call the director's office for its views on what Watson had said at the Domenici meeting two months earlier. Healy then conferred with Adler and Venter. She also had a conversation with Watson, in which he expressed his reservations about the patent application, but said he understood that it was prudent to have filed it as an interim policy. In a series of interviews and at a May 1992 meeting at the National Academy of Sciences, sponsored by the White House Office of Science and Technology Policy, Healy defended the patent application on several grounds. First, it would protect NIH's options, in case the patents were issued. Failing to file would irretrievably sacrifice any patent protection. She argued that the current decision might not be the best policy, but it protected future options. She conceded that "this is not a

statement that we believe that patenting this material is the proper thing to do now or for the future."[65]

Adler stated that the goal of the initial patent filing was a desire to advance the debate, not an "act of NIH economic imperialism."[57] He viewed the patent application as an experiment to see what discussion would follow.[57;66] What he had in mind was quite different from what actually ensued, however. The standard policy-making process was to solicit views from NIH's Patent Policy Board and to take actions, anticipating comments from those companies, trade groups, university technology transfer offices, and others who closely followed the relatively obscure field of biotechnology patent law. His office would typically take actions and then respond to comments coming in from this relatively technical and narrow constituency. The patent application on Venter's work, however, exploded far beyond this audience. NIH's intent was, in part to get comments on its action; it was overwhelmingly successful in this respect.

When Watson resigned as director of NIH's genome center in April 1991, debate about the NIH patent application became more separable from the intense drama unfolding between Watson and Healy. In August 1992, *Science* ran three companion pieces analyzing the NIH patent application. All agreed that the NIH decision to file patent applications had been reasonable, but the authors differed markedly in their tone and thrust.

Reid Adler reviewed the history of the decision and examined the precedents indicating that a patent might issue. He noted that early discussions about the genome project had failed to take account of how technology transfer policies and DNA sequence data would interact.[67] Responding to Watson's reference to monkey labor, Adler pointed out that the amount of effort involved in making a discovery was not necessarily a criterion for issuing a patent, and that in the United States, at least, patent protection was for the thing patented, not for any particular use. The central worry about failing to patent Venter's gene fragment sequences was that inaction might make subsequent patents on the complete genes impossible to obtain. By having a portion of the gene in the public domain, NIH might inadvertently thwart future patents on genes that might lead to important drugs and to gene therapy.

The Venter effort was scientifically formulated with one main purpose, to assemble a catalog useful in finding genes and discerning functional clues, not clearly a commercially viable use, but obviously a step in the direction of finding new therapeutics and other discoveries with commercial potential. The sequence from protein-coding regions also had other potential uses.[68] To obtain patent protection, NIH did not need to specify the ultimate use, but only a plausible one. The patent application claimed " 'enriched' or 'purified' full-length polynucleotide sequences, which are related to genes that do not exist naturally in this form." In a *Science* article that discussed the patent appli-

cation, Adler argued that "when full-length coding sequences can be obtained through even a dozen or more conventional sequencing steps without undue experimentation, a patent application disclosing partial gene sequences should entitle their discoverers to patent the full cDNA [complementary DNA] coding sequence."[69] Aside from the meaning of "full-length," clear enough.

The crux of the rationale, however, was that failure to patent could foreclose future commercial options: "If partial or full cDNA sequences without apparent biological function enter the public domain through publication, the sequences themselves would remain unpatentable even if applications were discovered later to genetic therapy or other emerging DNA-based therapies."[69] That is, if NIH did not patent its partial gene sequences, others might later be precluded from patenting any protein pharmaceuticals or other products related to those genes.

The trade organizations representing industrial biotechnology, the groups for whose benefit NIH's policy was crafted, all agreed the NIH patent application had a salutary effect in generating a policy debate. They differed, however, in whether patents should be permitted to issue and what policies NIH should pursue. In correspondence with Health and Human Services Secretary Sullivan and with Healy, the Pharmaceutical Manufacturers' Association opposed patenting of sequences with unknown utility, but urged NIH to pursue the existing filing until an international agreement on data sharing could be forged.[70–73]

The Industrial Biotechnology Association (IBA), representing mainly pharmaceutical firms and large biotechnology firms, commended NIH for filing the patent applications, but urged NIH to place into the public domain any patents for only partially sequenced genes and to license patents only when the complete coding region and biological function were known. IBA noted: "It is perceived as unfair to permit the Government to exercise complete control over a product to whose development the Government contributed little." IBA also pointed out that if the NIH patents issued, as well as similar ones from other research efforts, multiple parties could hold patents to different parts of the same gene, resulting in a thicket of infringement actions.

The scale of the patent applications was also troublesome. How would a small company know whether it needed a license or not? Each company would have to determine DNA sequences for products under development and compare them continually to the NIH set. If, as seemed quite plausible, patents issued in the United States, but not abroad, the patents could actually prove a disadvantage. The Cohen-Boyer patent, for example, obligated U.S. firms to pay a fee, but foreign firms did not because the patent was not valid there. Having to pay when foreign firms did not was hardly a competitive advantage. A countervailing argument, however, relied on control of gene discoveries for U.S. manufacture. Adler argued that patents, combined with a licensing policy giving preference to U.S. manufacturers, could at least give U.S. firms some advantage in the domestic market.[58]

IBA also expressed concern that the NIH patent application would displace action on other pending patents, while Patent and Trademark Office staff were diverted to examine the thousands of claims in the NIH application. Finally, IBA offered several options to assuage the policy dilemmas posed by NIH's patent application.[74]

The Association of Biotechnology Companies (ABC), another trade association with greater representation of small firms and also counting patent law firms among its members, supported the patent filing as "the only responsible course under existing federal law" and encouraged NIH's pursuit of similar claims in the future.[75] ABC focused on licensing, which should be given to one firm exclusively only when a full sequence and function were known, and should be nonexclusive otherwise.[75] ABC also sent letters to President George Bush and the Patent and Trademark Office.[76;77]

In a companion article, Rebecca Eisenberg noted that one distinctive feature of the controversy was that it was NIH, a federal agency, seeking the patent rather than a corporation whose private investment was at stake. She judged:

> The specific argument that patenting these inventions will promote investment in product development rests on two premises, both questionable but neither clearly wrong . . . [first] that NIH is entitled to claim patent rights that are broad enough to provide effective monopolies for firms . . . [second] that unless NIH obtains patent rights now, firms interested in marketing related products will not be able to secure effective monopolies in the future.[78]

She raised the chilling prospect that future patent rights might be undermined by the patent application if "NIH's disclosure is inadequate to satisfy the enablement standard for the broad claims in the application, yet revealing enough to render subsequent related inventions obvious and therefore unpatentable."[78] In other words, it could backfire. Disclosure in the patent application, however, would presumably be no more damaging to future patent rights than open publication would have been.

Patent lawyer Thomas Kiley was less circumspect in his analysis. His article did not condemn the NIH patent application, but instead urged that it become the vehicle for exposing deficiencies in the law, stating bluntly that "the trend of patent law in biotechnology is toward the debilitation of science."[79] He added:

> The NIH proposal for patents is only an extreme example of a widespread practice in biotechnology that seeks to control not discoveries themselves but the means of making discoveries. Patents are being sought daily on insubstantial advances far removed from the marketplace. These patents cluster around the earliest imaginable observations on the long road toward practical benefit, while seeking to control what lies at the end of it.[79]

NIH acted reasonably in filing the applications before a broad public debate, because there was simply no time to carry on such a debate. Moreover, if

NIH had not filed the patent application, under the 1986 Technology Transfer Act, Venter himself could do so if NIH waived its rights. This was more a theoretical concern than the driving force behind the decision in the case at hand, but it might prove more important in future decisions.

More generally, Kiley questioned the wisdom of such patents, especially the utility claims justifying them:

> To speak plainly, these are utilities concocted to carry the patents until someone finds out what the DNA is really good for. Since the real purpose of the applications is to control individual DNAs and thereby commerce in the proteins they encode, this approach, in my opinion, amounts to a cynical resort to deficiencies in the law concerning what utility is sufficient for patents.[79]

He argued that NIH had but one option to improve public policy, to "use them [patent claims] as a vehicle to ask the Supreme Court . . . if minimal contributions will continue to merit the grant of substantial monopolies."[79] Kiley also urged Congress to clarify the research exemption, so that NIH or another patent-holder could not shut down an area of research. While no university laboratory had ever been sued to block research, the increasing commercial attachments of such laboratories made such action more likely in the future, and the law did not explicitly provide any protection. NIH itself had a policy of permitting research uses, but that policy could change. In a more likely scenario, one university might sue another over patent infringement; universities and small firms might not be as restrained as NIH in pursuing their interests. The research exemption was created in case law and had narrow, but fuzzy boundaries. Kiley urged Congress to broaden and sharpen them.

Congress could also follow European precedent, allowing patents for new uses of known substances, "eliminating altogether NIH's excuse for its patent claims. . . . Here the work would be done by the group that did the hard work of inventing something more beneficial to the public than a mere catalog of mystery DNAs."[79]

Dr. Healy herself defended the NIH policies in the *New England Journal of Medicine:*

> NIH has taken the interim steps of publishing, and simultaneously applying for a patent to protect, the series of more than 2,000 partial gene sequences discovered in its laboratory. The rationale is not to make money, but rather to promote and encourage the development and commercialization of products to benefit the public and to do so in a socially responsible way.[80]

Healy noted that as a matter of policy, NIH would not charge for licenses for those engaged in research, as opposed to commercial development. Healy expressed NIH's willingness to seek patents only on well-characterized sequences if an international agreement could be forged to ensure that subsequent patents "for the full gene, its expression products, and their method of use" would not be endangered.[80]

A week before Healy's article was published, the Patent and Trademark Office (PTO) rebuffed NIH's patent application in a thirty-page document.[81] The patent claims were rejected on all three grounds—nonobviousness, novelty, and utility—and whether the description of the process was sufficient to enable others to produce the claimed sequences (enablement). The rejection had been subject to unconfirmed rumors,[82] but NIH did not make the response available or publicly acknowledge its receipt until Dr. Healy confirmed it at a hearing before the Senate Judiciary Committee on September 22.[82–85] At that same hearing, Craig Venter recounted how protecting the future patentability of genes was the main reason NIH had sought patents in the first place, and he proposed language that would make the NIH patent unnecessary by declaring in statute that disclosing part of a gene's sequence would not preclude later patents of the whole gene.[86] Healy supported this suggestion.[87]

One reason for the secrecy surrounding the PTO patent rejection was a battle raging within the Department of Health and Human Services. The department's chief counsel, Michael Astrue, had taken the unusual step of sending a letter to the PTO, asking that it suspend examination of the NIH patent application, because "I have concluded that a large portion of the applications do not satisfy the threshold legal requirements of an invention because they do not describe the function or use of the sequence."[88] The PTO sensibly pointed to the importance of pursuing the patent application to its logical conclusion, so that legal uncertainty could be reduced, and rejected Astrue's call for a halt to patent examination.[89;90] The PTO also appeared to chide Astrue for the way in which he raised the matter.[90] Once the PTO rejection was received by NIH, Astrue had also ruled that NIH could not respond, effectively killing the patent application if his orders were obeyed. (NIH was given three months to respond on the cover sheet of the August 20 PTO rejection.)[81] Healy was strongly opposed to Astrue's position, and Secretary Sullivan had not yet decided which faction to support.[91;92] The internal dispute between Astrue and Healy became public in early October, when *Science* and *Nature* ran news stories on the controversy.[91;92]

The rejection of claims from an initial patent application was not unexpected, and indeed Adler had predicted in his *Science* article that the initial decision would likely be a rejection.[69] NIH was taking considerable flak, as rumors of the PTO action spread through Washington, and yet NIH silence on the matter persisted. Theories of a devastating rejection of the patent application proliferated wildly, and suspicions of NIH's motives were rampant. Healy was in an awkward position, being ordered from above not to take action, but taking political heat for being surreptitious about her policymaking.

Healy's disclosure of the rejection was not in her written testimony at the September 22 Senate hearing, but she did volunteer the information in her oral statement. This action was taken despite removal of language about the PTO action during departmental and OMB review of her statement. Healy

thus courageously defied attempts to muzzle her and skated out on bureaucratic thin ice.

Prospects for the patent application itself were uncertain, and the subject of considerable speculation. The PTO rejected all twenty-four patent claims, saying they were "vague, indefinite, misdescriptive, incomplete, inaccurate, and incomprehensible."[81] But aside from that, they were fine.

Opinions about whether the PTO language was merely routine, whether it was actually an invitation to respond so as to move the application into an appeals process, or whether it was a devastating blow to prospects for the patent could all be heard. An initial rejection was quite common even when patents were subsequently issued. Ned Israelsen, the patent lawyer handling the application for NIH, believed that while the PTO rejection was longer and more detailed than usual, it appeared actually to be an invitation to respond, particularly in the sections covering utility claims. He concluded that the DNA sequences, and probably also their corresponding genes, "are patentable over the prior art."[93] Adler was convinced that ultimately the patent office would be obligated to follow the trend of U.S. law and issue a patent.[58] Several individuals who read the patent office's document interpreted it as far more than the routine initial rejection and read it as dooming any ultimate patent. Leslie Roberts of *Science* faxed the PTO document to several patent attorneys; none believed the PTO objections were insurmountable.[91] NIH did seek reversal of the PTO rejection, once Astrue left government; it also filed a new patent application for another 4,448 sequences on September 25, 1992.

Beneath the debate was a paucity of empirical data about the value of patents. Quite simply, no one knew and no one could really know. Only the results of years of patent decisions, litigation, and the complex workings of the global economy could answer the fundamental questions. The legal analysts, by and large, focused on the scope and economic return of the patent monopoly, but neglected the very high transaction costs of patent proliferation, with its toll of costly patent application, licensing and cross-licensing, and defense of patent rights. Every dollar that a research university spent for these purposes was likely to detract ultimately from the flow of dollars going into the research itself. With the prospect of 100,000 or more human genes and all the technologies to find them, characterize them, and manipulate them, the costs of obtaining the patents alone might ultimately be high, and the costs of defending those patents against infringement daunting indeed. The costs would hinge critically on the stringency of review in the patent examination process, the amount of subsequent litigation, and the ultimate scope of research subject to patent protection, all highly unpredictable factors. The costs might be low or high, but no one could predict this.

Research dollars fueled biomedical research. Most of the initial legal analysis seemed like naval strategy based on ship counts, with little attention to the importance of oil to move the ships around. If fuel didn't matter, the Japanese navy would have been far more effective in World War II. The neglect of

transaction costs promised to loom large in future discussions of patent policy. In the meantime, the captains steered in the dark.

Amid the furor over whether his scientific results could be patented, Venter took his science elsewhere. He resigned his NIH post on July 13, 1992, to head up a new Institute for Genomic Research.[94] He left NIH on good terms, responding to an opportunity to greatly expand his enterprise.[95;96] The new institute was funded under a $70 million, ten-year agreement with a corporate partner, Human Genome Sciences, Inc. The corporation, owned by the venture capital firm HealthCare Investment Corp., would retain commercial rights to discoveries emanating from Venter's research, although Venter would have rights to publish. Patent rights would go to Human Genome Sciences, and the laboratory would seek patents, in Venter's words, "on genes where we have substantial information . . . and where we feel there is a reasonable chance they will play an important role in diagnosis and therapy."[95]

The institute would go upscale even from the French Généthon, using state-of-the-art automation on a massive scale to zip through the genome. The institute ordered fifty DNA sequencing machines immediately, along with a host of Sun computer workstations and Macintosh computers, a supercomputer, and an enormous array of automated equipment.[50] It was the most audacious attack on the genome yet, replete with the highest of high-tech wizardry. Wallace Steinberg, who footed the bill as chairman of the board of HealthCare Investment Corp., referred to the dangers of international competition in guiding his decision. He hoped that the NIH patents, at least that fraction with unknown function, would be rejected, as it would remove any threat to subsequent patents for therapeutics and other products. But he justified the private-sector investment in Venter's work in nationalistic terms. He judged that NIH could not invest sufficient capital quickly enough to move as fast as the nation should demand:

> My God, if this thing doesn't get done in a substantive way in the United States, that is the end of biotechnology in the U.S. . . . There is a tremendous effort in France, England, and Japan. . . . If this becomes a race and if gene fragments become proprietary, then it is in the best interests of the U.S. and entities of the U.S. to file for patents."[94]

Venter planned to take several key staff members with him, so it seemed likely that the pace of research producing future continuations on the patent application would abate at NIH itself. But the issue would clearly surface elsewhere. In the meantime, one lasting legacy of the controversy was Watson's acrimonious departure from the NIH genome center.

20

Exodus: The End of the Beginning

THE CONFLICT BETWEEN James Watson and Bernadine Healy pitted two of the most powerful figures in biomedical research against each other. Watson was the most famous molecular biologist of his day and Healy the most powerful biomedical research administrator. Each was propelled by strongly held views, style, and personality into a battle from which each would emerge wounded, and with little to show in the way of improved policy. Watson left federal service in a conspicuous furor—no hollow man, he left with a bang, not a whimper.

Like Gettysburg, it was a battle that neither general had planned; they did not anticipate it would exact such a toll. Watson and Healy were drawn into battle by the force of events and timing. Controversy over patenting partial sequences of human genes unexpectedly became the battleground. On policy grounds, the fight was avoidable, but for the main characters there seemed no way out. The conflict was argued as a policy disagreement, but in the end it was not policy but information flow and personal style that drove Watson and Healy apart. Common ground could have been found—there were many positions that could accommodate both of their views—but mutual distrust obstructed communication and amplified disagreements. Healy's gaze fixed on the commercial promise of genome research and the increasingly strong mandate to NIH from Congress and the administration to make science into technology and economic power. Watson was determined to prevent a genetic gold rush that could undermine collaboration among research groups, not only within the United States but also, and more noisily, among genome projects internationally.

In the end, the battle was more important for its drama and symbolism than for any lasting impact on the success or failure of the genome project, whether measured scientifically or commercially. It was a transient focus for both Watson and Healy, although likely in the long run to prove only a footnote in either's career. The most important steps to establish the genome research agenda had already been taken. As Stanford geneticist David Botstein observed, "It was really crucial for the first four years to have Watson lead. . . . It was during this period that the agenda, plan, style, and funding level for the

project were established. . . . Now Dr. Watson's leadership is not as crucial."[1]

Watson had indicated from the start that he intended to direct the NIH genome office for only five years or so. He indicated publicly, at a genome advisory committee meeting four months before his resignation, that he was thinking seriously about stepping down. At that point, the DNA patenting controversy was smoldering, but it had not yet burst into flames. Watson disliked the pressures of his NIH job from the beginning, and he found them

Bernadine Healy was appointed NIH director in 1991, after the Human Genome Project was launched but while it was still a major source of controversy. Her dispute with James Watson over a complex web of issues led to his resignation as head of the NIH genome effort in 1992. With the advent of the Clinton Administration in the following year, she was relieved of her duties at NIH. *Courtesy National Institutes of Health*

particularly trying in 1991 and early 1992 as international tensions mounted, recurrent budget battles raged, and NIH's internal politics intensified in anticipation of and then with the reality of a new NIH director. Moreover, the NIH genome center's program was getting sufficiently large to demand the attention of a full-time director on site. The Watson-Healy contretemps prematurely ended Watson's federal career, but only by a year or so.

One positive aspect of the controversy was that it focused attention on the director's position at the NIH genome center and made finding Watson's replacement an important objective. By resigning, Watson became powerless to direct the selection. Yet Healy's reputation would be judged, in part, by whom she could attract to replace him. Watson's acrimonious exodus upped the ante, drawing attention to selecting a Moses for the genome project. This positive aspect, however, was overwhelmed by the far greater damage done to both Healy and Watson in the exchange.

The first public spat between Healy and Watson took place in 1985, predating the genome project. Watson complained about Reagan administration policy on regulations governing genetic technologies, making his point by noting that within the White House, "the person in charge of biology is either a woman or unimportant. They had to put a woman someplace."[2] He was referring to Bernadine Healy, deputy director for biomedical affairs in the Office of Science and Technology Policy.

Healy learned of Watson's remarks when staff from the Delegation for Basic Biomedical Research, of which Watson was an active member, called to apologize. As one of ten female students in her class at Harvard Medical School, she had experienced sexism directly. She had also been the victim of a cruel sexual joke while working years later at Johns Hopkins, at an especially vulnerable time amid a divorce, and she had pursued redress relentlessly.[3] Healy termed Watson's remarks "an offense to both men and women," while Watson replied that "anyone who heard me would know I meant it as a slap at the Reagan administration, not at Bernadine."[2] This became the first instance of a pattern, with Watson and Healy communicating their dissonance through the pages of public media rather than face to face.

If the full fury of the reaction had been known in advance, NIH might have chosen a different tack on the DNA patent application. While federal law would indeed require a patent application for an obviously patentable invention, there was arguably a weaker obligation for NIH to push the frontier of what might be patentable. Disagreement among competent patent lawyers about the NIH patent application meant either choice could be justified. It was one matter to abide by the law, quite another to push its limits. Yet if failing to patent might preclude patents on genes subsequently found, then the prudent course was to err on the side of filing the patent applications. Pursuing the patent application was arguably more a policy decision and less an exercise of mere obedience to federal law, but as an interim policy, it was likely to command wide support in the end.

Reid Adler, director of NIH's Office of Technology Transfer, asked an audience of genome researchers, "What better strategic message could you send to Congress to embellish your own funding requests than evidence of your commitment" to commercial application?[4] Healy was pursuing technology transfer at NIH as a major policy thrust. She had a long-standing interest in commercial applications of biomedical research and hoped to raise NIH's awareness of its importance. She served as chair of a panel that advised OTA in preparing five biotechnology policy reports from 1987 to 1990, and she remained interested in technology transfer issues and the role of biotechnology in the emerging global economy. The Bush administration was focusing attention on economic competitiveness, and biotechnology was one of its darlings. Healy could not afford to lose on the patent application issue. Watson did not believe he could back down either.

The biomedical research community divided into camps over the patent application. Venter was not part of the genome group close to Watson. Adler's office conferred with the genome office, but the policy decision already had momentum when the genome office was initially notified. Concern about future patent consequences drove the decision, not concerns about the patent application's impact on genome politics. Healy was not privy to the initial decision to file the patent application, as Adler considered it a matter of routine technology transfer and did not expect such public controversy. Healy was brought in only when the press began to raise the matter as a policy issue.

Healy later wondered why Watson did not inform her about the patent issue if it so upset him, and why he would go public first to complain about it. Watson acknowledged that he did not bring it to her attention, assuming that the Office of Technology Transfer must surely have done so for such a novel policy initiative, and judging that the patents were so unlikely to issue that the matter would dissipate of its own accord. The miscues were symptomatic of a general breakdown of communication. When Healy appointed Craig Venter, on the other side of the patent issue from Watson's genome center, to head up the NIH team to plan an intramural genome research effort at NIH in October 1991, Watson and others near him read it as an indication of whom Healy consulted for most genome advice. While Venter, Adler, and Healy all pointed to a broader group advising Healy on genome matters, including the genome center, those working with Watson did not feel they were consulted to the same degree as Venter or Adler. While planning and consultation were cordial and relatively smooth at the staff level, it was clear that communication between Watson and Healy was strained far more than usual for an NIH director and a center director.

Once established, this cleavage deepened into a chasm. Watson chafed and complained publicly about the patent application decision until he met with Healy in the fall of 1991, a few months after the Domenici meeting. He then agreed to desist from public dispute over DNA sequence patents, as the policy was still unsettled.[5] Watson deliberately chose to avoid Washington, not wanting to exacerbate tensions. Both Healy and Watson acknowledged a long period from fall 1991 into spring 1992 when they conferred little. Watson began to make private attacks on Healy. At many meetings, he railed about the lunacy of NIH's policy to his friends. Healy inevitably learned of Watson's attacks. Finding a policy accommodation became increasingly unlikely as the conflict escalated and became personal.

Beyond the issue of domestic technology transfer—the main concern of Adler and the NIH Office of Technology Transfer—a series of questions about adverse impacts on international collaboration flowed directly from deciding to file a patent application. One rationale for patent protection was to preclude a private firm or university, particularly a foreign one, from grabbing all the patent rights on human genes. A domestic company (or the domestic arm of a

foreign one) could indeed file a patent claim, but the main use of the sequence tags was to find genes or to give clues about gene function, achievements several steps removed from commercial application. There would be many more steps to commercial application, generally requiring substantial investments, before diagnostic and therapeutic products became practical. In other nations, patenting the sequence tags was unlikely to be possible. The main battleground would be over rights in the U.S. market.

The NIH patent application touched off an international firestorm. Alan Howarth, Britain's science minister, announced that the UK would file patent applications to hold its territory in the face of the American decision.[6] The UK Medical Research Council had previously considered patent applications, but had rejected this course under advice that the patents would not issue.[7;8] When the Americans filed an application, however, the UK felt compelled to do likewise. How the American and UK applications would be judged was an open question. It was clear that there was overlap between the fragments in the UK collection and Venter's collection.[4] How would such conflicting patent claims be sorted out? The rules governing such conflicts were generally established, but the number of such conflicts arising from a few patent applications was novel.

The UK and French governments joined forces to urge an international agreement that would stave off a patent rush.[6] Japanese scientists made clear they would not pursue patents for two thousand gene sequences deposited in their sequence database,[9] but the decision applied only to university scientists funded by the Ministry of Education and might not apply to industrial researchers or others funded from different agencies. Analysts believed patent applications for sequence tags would not pass muster in Japan and many other countries.[10] While the sentiment seemed to be dim for foreign patents along the lines of the U.S. application, there was nonetheless concern, often incoherently voiced, that U.S. rights alone would be sufficient to provoke a gold rush. Consternation over the NIH patent application initiated a regular traffic of diplomatic cables from U.S. embassies in Paris and London and from the U.S. representative at the Organization for Economic Cooperation and Development in Paris,[11] and it was suggested as a topic to be considered for a high-level multilateral treaty. The First South-North Human Genome Conference in Caxambu, Brazil, in May 1992, urged that "consideration be given to avoiding the patenting of naturally occurring DNA sequences. The protection of intellectual property should, in our opinion, be based on uses of sequences rather than on the sequences themselves."[12] This recommendation from scientists, however, flew in the face of American patent law.

Hubert Curien, French minister for research and technology, vigorously opposed the NIH patent application and obtained assurances from the European Patent Office that Venter's work could not be patented there. NIH nonetheless took steps to protect its options to subsequently seek European

patents,[13] by filing a patent application under the Patent Cooperation Treaty on June 19, 1992. That application expressed the intention to seek patents in Europe, Japan, and other nations. In a letter to *Science,* Curien cautioned that "attempts to commercialize basic data from the study of the human nucleotide sequence could be the death warrant of one of the most prodigious projects the scientific world has known."[14] Or it might not. The use of sequence information in securing patents of genes and gene products was well established. Human sequences were part of many patents already granted.

Just how to deal with the international tensions elicited by the NIH patent application was not clear. Watson proposed to hold an international meeting to discuss options, but Healy directly ordered him not to do so. Europeans urged an international treaty, and the Japanese were utterly mystified by the mixed signals emanating from America.

NIH lawyer Reid Adler explained that "it would be unfortunate if misconceptions about the patent system lead to a self-fulfilling prophecy that international research cooperation will be impaired,"[15] but NIH's patent application was an act that necessitated a foreign response. Adler pointed out that *research* need not be impeded, as NIH's policy was to permit unrestricted use for research purposes. To the degree that other nations were investing in genome research even partly in hopes of commercial promise, however, the basis for international conflict was real. Cordoning off research use as a free zone did not avoid the policy dilemma facing foreign governments if U.S. researchers sought patents and foreign scientists did not.

Bernadine Healy addressed the international implications directly, and acknowledged the need for international agreement.[16] The international objections to NIH's policy were couched in sanctimonious rhetoric, and may even have betrayed a misunderstanding of what was at stake, but the danger to international scientific cooperation was nonetheless genuine. This was not because patents would shroud the genome in secrecy, but because each country wished to translate genome research into commercial payoff. The genome project was held out as a scientific and *technical* enterprise with commercial spinoff.

If one country controlled patents, even if only in the United States (the largest single market), others could not. Every nation viewed biomedical research as linked to commercial development in biotechnology. To the extent that the genome project was supported as pure science, and if an international agreement could be forged to enable free sharing of data, then collaboration could indeed be preserved. But absent such an agreement, each nation had strong incentives to file patent applications independently, and not to share the DNA sequence tag data until such applications were filed. The incentive for a gold rush hinged on the act of filing a patent application, not whether the patents eventually issued. To preserve their interests, foreign competitors had to assume that patents might issue to the NIH or others, and the only defense

was to file applications of their own—and to cover the territory more swiftly than U.S. investigators. Filing patents in their home country would establish the date for any future disputes over U.S. patent rights.

On the home front, Senator Al Gore questioned NIH's wisdom:

> These patent applications by NIH are not a defensive maneuver, they smack of a first strike, a preemptive strike that has predictably caused counterattacks by other governments and possibly by private researchers as well. . . . Unfortunately for the future of the human genome project and international cooperation in science, NIH's actions speak much louder than its words. The very act of filing these applications . . . is universally viewed as an attempt to corner the market on human genetic information.[17]

The cost of doing the science itself could go up. Unfettered competition, with a delayed flow of data while intellectual property rights were staked out, had real dollar costs. The expense of duplicating gene mapping efforts, when different groups did much the same work in competition—with all the spoils going only to the winner—was being demonstrated in the cases of corn and rice genomes. The overall cost of deriving the same amount of information was many times higher, because everyone had to do the entire genome independently. The fragile cooperative framework for the genome project had prevented much wasted effort, by putting groups in touch with one another for the yeast, *C. elegans,* bacterial, mouse, human, and fruit fly genomes.

The importance of patenting to commercial biotechnology, however, was undeniable even in the absence of solid empirical data. While there were few studies of how patents influenced private research and development investment or subsequent product development, it was clear from the history of the pharmaceutical industry that patents were critical. This still left open the question of how best to preserve intellectual property rights while enabling research collaboration.

An international agreement was desirable, but a daunting prospect, as it would require resolving in treaty language just those points of uncertainty that provoked the controversy in the first place, not just within the confines of U.S. law, but among nations. A narrow provision that enabled patents on a full-length sequence even if part of the sequence had previously been published or patented—along the lines proposed to fix the patent dilemma domestically—might solve the immediate problem at the international level as well, but there were much broader issues at stake. International patent standards pertaining to molecular genetics would also have to address the scope of the research exemption, criteria for establishing priority of patent rights, publication practices after filing, whether there was a grace period after public disclosure before applying for a patent, and other vagaries of different nations' patent policies. The DNA patent issue seemed likely to become but a small part of a much larger effort to harmonize international patent policies. An international agreement was desirable, but it was unlikely to be forged quickly, and might not come in time to forestall a gene patent rush.

Scientists helped define the problem, but they could contribute little more than background technical information relevant to the legal rules. The law and not science would decide how technical information fit into the intricate structure of the national and international economy. Congress would write the rules, patent examiners would grant or reject patent claims, patent lawyers would litigate, and judges would decide individual cases. National governments might meet to craft agreements. Over time, the outcome might become clear, but it would be quite some time, and scientists would for the most part be observers and advisers, not policymakers.

The genome project was sold, in part, as a huge international collaboration, and coordination with researchers abroad was a major preoccupation of NIH's genome office. The force driving decisions about the NIH patent applications, however, was technology transfer. The genome office and the NIH director's office came into conflict in part because they were attending to different problems.

Disagreement over DNA patenting was the most conspicuous irritant, but there were many other sources of conflict between Watson and Healy. Frederick Bourke, a former squash champion from Connecticut whose business interests turned to the commercial promise of DNA sequencing, helped to dislodge Watson. In fall 1991 and into 1992, Bourke made overtures to several genome researchers. He hoped to set up a company in Seattle, Washington, to do genome research on a massive scale with high technology. Bourke aspired to do with private American funds, and with an eye to future commercial benefit, what the French had pioneered with Généthon and Craig Venter would months later begin to establish at the Institute for Genomic Research in Maryland.

Bourke's basic idea was to use pilot projects to develop sequencing capacity, and to use that sequencing capacity to pursue commercial leads. Bourke began to negotiate with John Sulston in the UK and Robert Waterston in St. Louis about doing the *C. elegans* sequencing project under his patronage. This project had been among the first large-scale mapping and sequencing efforts under the genome banner and was perhaps the most successful transatlantic collaboration, producing results at an impressive clip.

Watson met Bourke for the first time on January 24, 1992, and the two quickly developed a strong mutual distaste.[18] Bourke characterized Watson as "reactionary"[19] and Watson privately professed his strong distrust of Bourke. Watson interpreted Bourke's overtures to Sulston, Waterston, and their colleagues as a direct threat to a highly successful transatlantic collaboration, endangering a genome research project likely to bear early fruit. Watson viewed Bourke's efforts as a torpedo aimed at his flagship.

At the same time, a genome research center affiliated with the University of Washington in Seattle was forming, based on a $12 million donation from William Gates, cofounder and CEO of Microsoft Corporation.[20] Microsoft's

assets skyrocketed over two decades, and it quickly became one of the wealthiest corporations in the nation. Genome research became one Microsoft's beneficiaries. Gates, who had quickly become an immensely wealthy business leader, was intrigued by the natural alliance between computers and DNA analysis and put up the donation to bolster research at the major university nearest to Microsoft's headquarters in Redmond, Washington.

Gates's Seattle venture was entirely separate from Bourke's, established through the university. It proved more successful, netting two giants of genome research—Maynard Olson from Washington University in St. Louis and Leroy Hood from Caltech. Applied Biosystems, Inc., was to supply the instrumentation. (Applied Biosystems merged with Perkin Elmer months later, bringing together two of the most important biotechnology instrumentation companies.)

Hood initially helped found the Bourke venture and was already serving as a Bourke adviser.[20] Bourke's separate institute was to be started with $50 million, collaborating with the University of Washington genome center. Young scientists would be attracted to the facility, working shoulder to shoulder with two of the field's luminaries in a high-tech genomics heaven on the shores of Lake Washington.

Watson was working on both sides of the Atlantic to preserve the existing *C. elegans* collaboration. He spoke with representatives of the Wellcome Trust in London, the UK Medical Research Council, and his extensive set of British contacts. Government officials and private science philanthropies were also brought into the fray; British science administrators, in particular, did not wish to see further UK-to-U.S. brain drain, with another highly touted research team leaving England. Aaron Klug, Nobelist and director of the MRC molecular biology laboratory in Cambridge, regarded Bourke's offer as a hostile takeover bid, and other MRC officials complained loudly.[19] As Bourke continued discussions with the *C. elegans* researchers, the government grant that supported work in Cambridge expired. Bourke agreed to Sulston and Waterston's demand that all their work would be in the public domain, but distrust of the venture nonetheless ran high among outside observers.

With his London contacts, Watson discussed the need to keep a vital and open *C. elegans* collaboration between the United Kingdom and United States, along with other issues unrelated to the *C. elegans* collaboration—the NIH patent application, how to share support of databases, and revitalization of international coordination more generally. The Wellcome Trust, a large private philanthropy already involved with genome research through various scientific contacts and the Human Genome Organization, stepped in with a £50 million, five-year grant to support the *C. elegans* project and to expand British genome research on other organisms and on informatics.[21;22] In the end, Sulston and Waterston continued their collaboration, with more resources and strengthened international reputations. The Wellcome Trust and MRC took steps to establish a major new facility in Hinxton Park, south of

Cambridge, fittingly named the Sanger Centre. (Fredrick Sanger, whose philosophy was to approach molecular biological function through the study of ever larger structures, was a pioneer of protein and DNA sequencing—see Chapter 4. His approach not only helped guide research in the UK, but was also carried through Maynard Olson's voice on the National Research Council committee—see Chapter 10.) Sulston was to direct a substantial genome research group at the Sanger Centre, which also hoped to become the major informatics center for genetics in Europe. Watson had won the battle, but Bourke struck back.

Bourke spoke to Healy, and followed up with a letter detailing his complaints about Watson. In the February 25, 1992, letter, Bourke recapitulated: "In our recent conversation, we discussed the resistance I have encountered. . . . I believe that much of this resistance originated with Dr. James Watson of your staff."[18] Bourke cited a conversation with C. Thomas Caskey, who had expressed reservations about joining Bourke after speaking to Watson. Bourke also invoked the names of Leroy Hood, Charles Cantor, and John Sulston as corroborating instances of Watson's interference. Leroy Hood also called Healy to complain about Watson's lobbying to scuttle the Bourke venture. Others also began to call Healy's office to complain about Watson, many alleging conflicts of interest.[5]

Bourke asserted that his commercial interests were thwarted by Watson and questioned whether Watson had the best interests of the nation at heart.[18] Bourke cited Caskey's account of Watson's rendition of a meeting with Glaxo officials to torpedo the venture. This was not straight from the horse's mouth, and its implication was false. Watson had indeed spoken with Glaxo officials, to whom he was a regular adviser, but he had addressed the issue of DNA patenting, before he was even aware of Bourke's interest in the *C. elegans* project.[23;24] While Bourke's torpedo may have passed wide of the mark in its first pass, it ultimately circled back and found Watson's hull.

Bourke's allegations were short on proof and long on hearsay, but his letter was enough to precipitate a Healy inquiry. Healy was quite sensitive on matters of financial conflict of interest, having herself been publicly accused of a conflict for holding stock in the biotechnology company Genentech. Healy was one among many clinicians and scientists whose ownership of stock in Genentech raised eyebrows regarding clinical trials of its blood-clot-dissolving drug, tissue plasminogen activator (TPA). Healy did not purchase the Genentech stock until several years after the TPA trial ended, and she had left the sponsoring institution, so it could not affect the results; but she did purchase the stock before her former colleagues published the trial's results.[25] The episode made an impression, and Healy was subsequently instrumental in putting together strict guidelines to prevent conflicts of interest in clinical trials.

After Bourke's letter and other calls about Watson's possible financial conflicts, Healy asked for the files on Watson's financial holdings, inspected them, and forwarded them to James Mason, the assistant secretary for health.[5;26–30]

A few months later, Watson was called into the office of Jack Kress, who handled conflict-of-interest issues for Mason. Watson first saw the Bourke letter in Kress's office. Watson had disclosed his holdings in several previous reviews,[27–29] but the Bourke letter provoked another look. In Watson's files, Healy found an electronic mail message from NIH counsel Rob Lanman to her predecessor, acting Director William Raub, that raised questions in her mind.[30;31] This memo was referred to Kress, who did not act on it.[32]

Watson was outraged that he first heard about a letter from Kress rather than Healy. Healy responded that she was merely complying with departmental policy on matters of ethics, on Mason's advice. After his meeting with Kress, Watson began a series of calls to a circle of confidants announcing his intention to resign. He believed that the way the Bourke letter had been handled and the inspection of his financial background were bureaucratic moves to get rid of him.

Kress and Michael Astrue, chief counsel for the Department, assured Watson that there was no conflict of interest as far as he was concerned, although there were a few matters of concern. Kress said he intended to recommend that Healy sign a waiver enabling Watson to retain his holdings. Healy's office, however, expressed great concern about a potential conflict of interest to *Nature*[33] and told the *New York Times* that Healy "would rather not resolve the matter by giving Dr. Watson a waiver," although the suggested waiver "was no more broad and dramatic than Healy's own waiver."[34] Healy did not want to sign waivers, but was willing to have her superior, James Mason, do so; Mason was not willing to sign waivers that Watson's direct supervisor, the NIH director, would not.[5] In the end, Watson met again with Astrue. After a long conversation, Watson concluded that he was boxed in. While he might win in the end, it could prove a nasty and highly public battle with Healy, and it would be simpler for him to resign.[23,35]

Kress openly defended Watson to reporters, saying that "this is very common, nothing out of the ordinary. . . . I made it very clear to him that in no way, shape, or form did I find anything improper about anything he was doing,"[36] and "after talking it over with Dr. Watson, I was satisfied that there was no conflict . . . there is no ethical reason for him to leave."[33] Yet on the same day, Johanna Schneider from Healy's office told the *Washington Post* that "Dr. Healy does not have the luxury of ignoring ethical questions, even for a Nobel Prize winner."[37] Accounts emanating from two points in the same department of government were in clear opposition.

Watson's interpretation that he was being sacked turned on several factors. One was the fact that Kress, who usually handled ethics matters and to whom Healy had referred the matter, believed there was no conflict of interest but Healy apparently did. Both Kress and HHS chief counsel Astrue had assured Watson that the conflict-of-interest waiver he would need was no broader than that held by most senior NIH administrators, including Healy herself. Watson also called a fellow Nobel laureate, Daniel Nathans of Johns Hopkins. Healy

had discussed the situation with Nathans, whom she knew from her John Hopkins days. Soon after Nathans's conversation with Healy, Watson contacted him. Watson concluded from this conversation that he was being subtly told to leave. He told the *Washington Post* that Healy "does not want me."[38] Another part of the crescendo was a March 25 hearing before the House appropriations subcommittee.

Watson and Healy appeared together to justify the genome budget request. The process of formulating a budget for the genome center had been frustrating for all concerned. It was Healy's first full budget cycle as NIH director. She had also launched a strategic planning exercise for the entire NIH. Healy's initiative to bolster trans-NIH planning was in line with a pair of reports on NIH structure and management, prepared by Institute of Medicine committees in 1984 and 1988.[39;40] The strategic planning process was controversial as it unfolded, for reasons unrelated to genome politics. Rancor centered on the process rather than the need or intent. The research community was highly suspicious of a process they perceived as guided by NIH bureaucrats rather than scientific experts. Regardless of the outcome or which faction was closer to the truth, one feature of Healy's directorship was clear—she would play a much stronger role in budgeting of the individual institutes than had her predecessors.

The genome budget was prepared amid the patent policy disagreement between Watson and Healy and further hampered by lack of communication. A symptom of the difficulty was a briefing set up by Healy's office, which disrupted a meeting planned between Watson and Rep. John Dingell, chairman of the committee that authorized NIH (including the genome center). In preparation for House hearings on NIH's budget, Healy scheduled briefing sessions with senior managers at each NIH institute, center, and division. The meetings fell off schedule the morning the genome office was on the roster. Watson and the genome center staff were put on hold for several hours, which forced Watson to cancel the Dingell meeting, an appointment he had labored to secure for many months. The press of time before the appropriations process limited flexibility in Healy's schedule. Watson was only in town for a day, and the Dingell meeting could not be readily rescheduled. While it was understandable and clearly not deliberate, the schedule conflict was just another reminder to Watson of his uncharacteristically subordinate position in the federal hierarchy. From Healy's perspective, it was another instance of the difficulty of having a major program directed by a person who was only occasionally present.

Watson avoided reporters for many months, having agreed in the fall not to publicly criticize NIH policy on the patent controversy[41] and to clearly distinguish his personal views from official NIH policy when commenting on it privately. At the March 25 hearing, Representative William Natcher, chairman of the subcommittee, asked Watson point-blank: "What do you think of NIH's decision to seek patents on several thousand gene sequences?"[42] Watson

began to temporize: "The patent law doesn't really cover DNA. It was invented before DNA was discovered. There is the possibility that, in fact, DNA can be patented. That will be decided by lawyers and judges." But he then answered directly: "The second question is, if it is patentable, is that a good thing for the human genome [project and] the biotechnology industry? This is a debatable issue. I think it would be better if we did not patent sequences that you don't understand. Once you understand what it does, then I am in favor of patenting."

Watson then opened the floor for his boss. "I am not a lawyer. I am not responsible for the decision. I think you should ask Dr. Healy her views on this point."

Natcher did. Healy responded with a statement of interim policy:

> I think the debate on DNA patenting is inevitable. Every time we have moved into the issue of patenting some aspect of genes—transgenic animals, genetically engineered microbes, and so forth—there has been an enormous debate and question. I think a debate on DNA, for which we have limited knowledge, was inevitable. NIH policy has been, after many months of considerable discussion and review of the issue, to take what we view as a protective posture. It is not to make a statement as to whether or not it is good or bad to hold a patent on this material under these circumstances, but rather a position that until we have a position of legal harmony and legal certainty; until we have international agreement on what is patentable and what is not; and until we know what the consequences of the patenting or licensing would mean, and what it means if this information is put in the open literature without any kind of intellectual protection—until those issues are resolved, NIH is taking a protective posture.[42]

This was a dangerous matter to bring unresolved before the House appropriations subcommittee. Either policy choice—to seek or not to seek patents—could be defended; the process that produced the interim NIH policy, however, had not yielded consensus among the major players, and indeed Watson and Healy were on sufficiently bad terms that they had not discussed the patent application for many months. It festered as an open sore, a major controversy in the scientific press, brought untreated before the congressional group with enormous power over NIH's budget. Given the indirect routes of communication between them, it is not surprising that Watson read Healy's motives as hostile, and vice versa.

NIH could have found policies to accommodate both future commercial opportunities and the need for information flow and scientific collaboration. Options for such accommodation abounded—international agreements, statements about how the patents would be licensed if issued, a clearer definition of what research uses would be exempt from the patent monopoly right, or agreement to pursue a new form of intellectual property protection. Each of these avenues could satisfy both Watson's and Healy's policy goals. Indeed, Adler's article explaining NIH's patent decision suggested that "perhaps patenting and licensing optimally should be pursued only for complete coding portions of a gene for which a generalized biological function seems appar-

ent,"[15] a position indistinguishable from Watson's except for the "perhaps." Adler's point was that this could be decided only after careful review, and that failure to file applications on the partial gene sequences would have been irreversible. Adler raised the issues with senior genome advisers within NIH and in the university community after the controversy hit, but found them too hostile to have a meaningful discussion. Adler believed NIH could still control when and whether the patents finally issued; it could exercise no control if patent applications were never filed.[15] There was common ground, but it was being fought over, not cultivated. They beat their plowshares into swords.

On March 26, 1992, a day after the House appropriations hearing, Watson called a circle of confidants, telling them he had to resign. He privately vowed never to appear before a congressional committee again under conditions where he would feel personally compromised. The conflict had crossed a threshold, violating his personal sense of integrity. He felt that juggling his financial holdings to eliminate Healy's concerns about conflict of interest would merely delay his departure. He told reporters from the *Washington Post* he was willing to sell his stocks: "I could divest most of them, but it would be pointless."[38] He believed another bureaucratic burr would be placed under his saddle, and then another, until he left. Watson felt that while Kress had been careful to say there was no irresolvable conflict of interest, Healy's office had set him up for a public flaying.[24; 35; 43] Healy felt that the conflicts were real and required either Watson's resignation or divestiture.

From Watson's perspective, the alternative to his resignation was a protracted and public legal battle. He believed he would continue to be attacked in newspapers. Many of his friends urged him to stay on through the budget cycle, and he vacillated for several weeks, while press reports speculated on his imminent resignation.[33; 36; 38] Following the meeting with the head counsel for the Department of Health and Human Services, Michael Astrue, he decided to resign very quickly. On a Friday at 1:00 P.M., April 10, 1992, Watson resigned.[41; 44–47] No face-to-face Watson-Healy meeting ever took place to discuss the resignation. In a move pregnant with symbolism, Watson resigned by fax from his office at Cold Spring Harbor Laboratory, his safe haven.

In the wake of Watson's resignation, press reports dealt with the conflict-of-interest issue, but centered on Watson's contribution to the project and the rough treatment he had received at Healy's hands. *Science, Genetic Engineering News,* and a *Nature* editorial were largely laudatory of Watson.[1; 41; 46–48] A *Nature* editorial, taking a more pro-Watson stance than its accompanying news articles, ventured that "Dr. Bernadette [sic] Healy . . . has wanted Watson out of the Human Genome Project. . . . But Healy will find she has damaged herself more than she has hurt Watson."[20; 44; 48]

Within hours of Watson's resignation, Healy released a diplomatically phrased statement expressing regret that Watson had resigned and naming

geneticist Michael Gottesman, from the intramural research program at the National Cancer Institute, acting director. She had invited Gottesman into her office to offer him the position and had made it clear he had to make his mind up. In her public statement, Healy reiterated regret at Watson's decision to resign. This was repeated several weeks later at a May 5 press conference, staged to introduce the press to Dr. Gottesman and to clarify NIH's continuing commitment to the genome project just before the annual genome research meeting at Cold Spring Harbor Laboratory.

In the end, both Healy and Watson emerged diminished. Watson was stripped of his official capacity as head of the NIH genome program. Healy alienated a powerful figure in science. The genome project itself carried on, now robust enough to withstand such buffeting. The Watson-Healy rift seemed likely to heal at least partially. Watson, in his annual report for Cold Spring Harbor, acknowledged the disagreement with Healy over DNA patenting, but attributed his inclination to resign more to his "inability to be the active manager the Project now needs."[49] He proffered an olive branch, noting that "there is every indication that Dr. Healy will desire to quickly appoint a scientist of major accomplishments to replace me. Naturally, I will continue to remain a strong proponent of genome programs and if asked, will enthusiastically give the new director my assistance."[49] For her part, Healy expressed personal affection for Watson, although giving no ground on the conflict-of-interest issue. She was convinced that the genome project was the better for her actions. In the intricate web of personalities, ideas, and issues that created the genome project, Watson's resignation was yet another *Rashomon*.

The Watson era of the genome project ended as it began, subject to the complex interplay of scientific objectives, positions of political power over biomedical research, and contending visions. The purpose of the science was to create precise information about human genes and technologies to explain genetic mysteries. Pursuing that purpose, however, was an inherently political process. It involved individuals vying for power to make decisions—players in the drama by dint of their positions in the federal government and in the scientific community.

The science of the genome project built on facts; its history, on stories.

Epilogue

THE JANUARY 1, 1993, issue of *Science* announced that Francis S. Collins of the University of Michigan had agreed to direct the NIH genome program,[1] confirming rumors that had persisted since midsummer. Collins agreed to join NIH on condition that a significant intramural genome research capacity be created on the NIH campus in Bethesda, Maryland, so he would not have to give up active laboratory work. Collins agreed to make the move despite a cut in pay and the disruption of one of the most secure scientific empires in human genetics. Several members of his group, including himself, were funded by the Howard Hughes Medical Institute. This highly prestigious and financially stable base was buttressed by an NIH-funded genome research center linked to the University of Michigan.

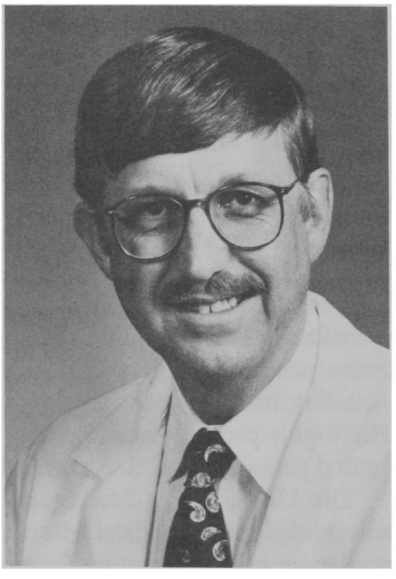
The University of Michigan combined one of the best state-supported universities with a medical school that had chosen soon after World War II to emphasize human genetics. Stanford geneticist David Botstein, for one, believed that his unusually broad and deep training at Michigan—with exposure to excellent molecular biology and world-class human genetics, including population genetics—gave him the requisite background to prepare him for the 1978 insight about the importance of a human genetic linkage map.[2] Construction of just such a map helped spawn the revolution in human genetics that began in the 1980s.

Why would Collins leave such an enviable position to direct a federal program? His answer: "Because there is only one human genome program. It will only happen once, and this is that moment in history. The chance to stand at the helm of that project and put my own personal stamp on it is more than I could imagine."[1]

Recruiting Collins was a major coup for NIH director Bernadine Healy.[3] She had to go to considerable lengths to secure precious laboratory space on NIH's campus, displacing other research groups and thus engendering strong antipathy among those who had waited for years to get it. Healy's own future became quite cloudy with the election of President Bill Clinton, and she announced on February 26, 1993, that she would leave the NIH directorship by June 30.[4] In her statement, Healy singled out among the major initiatives she

hoped would continue after the end of her two-year tenure the NIH strategic plan, women's and minorities' health initiatives, recruitment of scientific talent, and an expanded Human Genome Project. It seemed likely that attracting Francis Collins, as part of the expansion of the genome project, would be an important part of her legacy.

Collins was on everyone's short list for the job, probably the only person about whom that could be said. His scientific qualifications were unques-



Francis S. Collins was successfully recruited by Healy to head the NIH genome program, following Watson's resignation. Collins, a leading researcher in the field, had been at the University of Michigan, where he directed the team that found genes for several hereditary diseases, including cystic fibrosis. *Courtesy National Center for Human Genome Research*

tioned. Together with Lap-Chee Tsui of the University of Toronto, Collins had directed the team that first found the cystic fibrosis gene,[5–7] and his was one of two teams that found the gene for neurofibromatosis, type I.[8–11] (The other group was directed by Ray White at the University of Utah; while the two groups had initially collaborated, they parted company, only to cross the finish line almost simultaneously.) Collins was an integral part of the collaborative team organized by Nancy Wexler to search for the Huntington's disease gene,[12] and his group was in the hunt for an early-onset familial breast cancer gene mapped to chromosome 17, near the neurofibromatosis gene. Collins and his group were thus in the thick of some of the most conspicuous gene quests. That work, in turn, was coming to define a deep current in the mainstream of biomedical research.

Collins continued to work in medical genetics and genetic counseling, one of but a few first-rank molecular biologists to maintain clinical skills. The clinical work gave him an instinctive feel for the impact of genetic information on families. He had a keen appreciation of and support for the ethical, legal, and social issues program. He had followed the ELSI working group's efforts

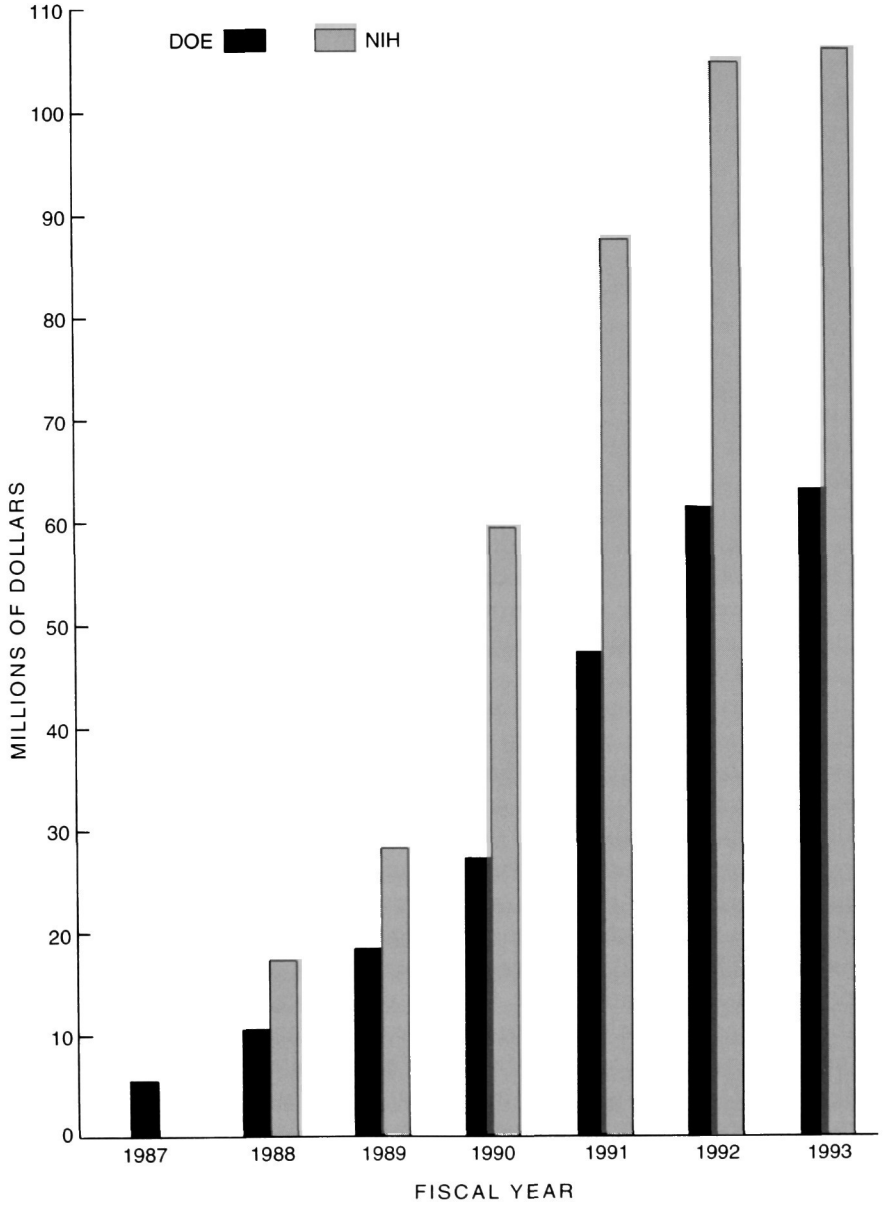
on cystic fibrosis pilot-testing programs. People who worked closely with him at the University of Michigan were tracking several issues in close collaboration with the ELSI research program, especially those related to Huntington's disease and breast cancer.

Collins was also rare among genome scientists in accommodating religious interests. He was comfortable speaking publicly about his religious beliefs, as when he spoke to a group of theologians at a March 1990 conference, noting how his Christian values reinforced his commitment to biomedical research.[13] This breadth of clinical and scientific background and appreciation for the broader context in which the science was being performed made him an ideal candidate to direct the NIH genome research effort.

Even as Collins began to grab the reins, the NIH part of the genome project was on its way to becoming a fully entrenched part of the bureaucracy. The NIH authorization bills, S. 1 in the Senate and H. R. 4 in the House, both formally authorized the National Center for Human Genome Research. The genome center had been created by administrative action within the Department of Health and Human Services, with agreement of the appropriation committees. The new authorization statute gave the genome center more permanent status, so that a future Secretary of Health and Human Services could not simply dissolve it. The bills also mandated that at least 5 percent of the budget go to the ELSI program. The House and Senate NIH bills were put on the fast track in 1993, largely because they had been vetoed by President Bush the previous year over provisions concerning fetal-tissue research. Several members of Congress promised during the 1992 presidential campaign to pass the law early in a Clinton administration if Bush lost the election. Bush did lose, and the NIH bill did indeed receive early attention from Congress. The Senate went so far as to introduce NIH authorization as its first bill for the new Congress. President Clinton signed it into law as Public Law 103-43 on June 10, 1993.

This special attention to NIH authorization ironically posed a problem for Collins. He aspired to transform the National Center for Human Genome Research into the National Institute for Genomics and Medical Genetics, making clear its broad mandate and conferring full institute status upon it. Collins was not yet the director of the genome center as the bills were transiting Congress, however, and AIDS research and fetal-tissue research provisions commanded almost all the political energies of the bills' congressional champions. He was thus poorly positioned to succeed in effecting last-minute changes in the NIH bill. The NIH genome center would have to wait a few more years, until the next authorization cycle, before it could become an NIH institute by statute. (An agreement to pursue institute status through action within the administration, however, was part of the recruitment package that brought Collins to NIH.)[14] When Healy resigned as NIH Director on June 30, Ruth Kirschstein replaced her as Acting Director on July 1, 1993. As the transition began at NIH, David Galas at DOE also announced he was departing, to

U.S. budget for genome research grew sharply from 1987 onward, before leveling off at a total of about $170 million per year, as shown in this bar chart, representing the two main U.S. programs. Figures for the Department of Energy (DOE) are for its Human Genome Initiative. The 1987 budget reflects funds reprogrammed from other areas; earmarked budgets within DOE began in 1988. The National Institutes of Health (NIH) figures for 1988 and 1989 correspond to earmarked funds spent at the National Institute for General Medical Services and coordinated by the Office for Genome Research, part of the NIH Director's office. The National Center for Human Genome Research was established at the beginning of fiscal year 1990 and acquired its own budget. Figures for 1993 are estimates based on congressional appropriations. Figures for 1988–1992 are based on appropriations, adjusted for actual expenditures.



become part of the scientific team at Darwin Molecular, Inc., a new biotechnology company based in Seattle. In August, President Clinton announced his nomination for NIH Director: Harold Varmus, a Nobel laureate cancer researcher from the University of California, San Francisco.

While the NIH genome center was attaining statutory sanction, the genome project as a whole became the exemplar of yet another major policy debate, this time over commercial investments. Private corporate investment in genome research became fashionable in 1992 and 1993. The prospects for attracting private capital had changed dramatically in five years. Whereas Walter Gilbert had great difficulty in finding venture capital to launch the Genome Corporation in the spring of 1987, a symposium devoted to solicit interest among pharmaceutical firms, organized by Craig Venter and Gilbert, drew a respectable audience in September 1990.[15] Translating intellectual interest into direct financial investment, however, took several more years. By early 1993, in contrast, many of the most prominent genome researchers were being approached by venture capital firms, major pharmaceutical houses, and other sources of private funding. The Institute for Genomic Research in Gaithersburg, Maryland, was but the largest among many new privately funded ventures with working capital of over $70 million. It was a nonprofit entity attached to several for-profit corporations under a corporate umbrella. The for-profit arm was Human Genome Sciences, Inc., which in May 1993 appointed William Haseltine CEO, and announced an alliance with Smith-Kline Beecham valued at over $130 million. Other ventures were organized as for-profit companies to do genome research. Frederic Bourke, whose interest in genome research indirectly contributed to Watson's resignation, resurfaced as a major investor, and there were dozens more.

Science devoted a feature article to the emergent private investments in genome research, raising questions about whether the genome project could be both a public good and a recipient of substantial private investments.[16] Could the most prominent genome researchers disclose their data quickly and also honor their commercial commitments? Questions about conflict of interest had become much more prominent throughout biomedical research, as the scope of commercial research investment grew and scientists shed their vows of poverty. While the genome feature article was only one among a half-dozen pieces that *Science* ran on conflict of interest and commercial aspects of biomedical research, it nonetheless placed the genome project once again in the spotlight of an emerging controversy. As had happened in so many other policy areas, the genome project became the focal point in a more general debate. The ELSI grant money distinguished the genome research effort from some of the other foci of attention over conflict of interest, as it enabled NIH to give a grant to David Blumenthal of Massachusetts General Hospital to gather empirical data about the extent and impact of private financing on genome research.

The influence of private funding was by no means confined to the United

States. The United Kingdom, the only other country to make commensurate genome research commitments, also had a heavy infusion of private funds. Indeed, the private support of the Wellcome Trust far outstripped the government funding through the Medical Research Council. The group charged with preparing an analysis of UK genome research included representatives from the three largest pharmaceutical firms—Glaxo, ICI, and Smith-Kline Beecham—and the Wellcome Trust funding came from the foundation arm of pharmaceutical giant Burroughs-Wellcome.[17] In France, the most conspicuous genome effort was the collaboration between Généthon and AFM, the muscular dystrophy association, both largely privately funded, although not directly tied to corporate interests. The nature of most private investment abroad, therefore, was different in intention, although there were signs that other governments hoped to entice investment by pharmaceutical firms. Canada and the UK, in particular, were clearly making overtures to private drug companies.

The increasing role of private funding of genome research, both corporate and nonprofit, was an indicator of developments throughout biomedical research. Because genome research was conspicuous, and entailed state-of-the-art instrumentation and first-rate talent, and because finding genes might be a short path to possible new pharmaceuticals, genome research attracted venture capital.

At the same time, biomedical research in general, with genome research as a specific instance, had attained sufficient national importance to become a political issue. The genesis of the genome project was itself a demonstration of this fact. It was created not by citizens concerned about cancer or heart disease or even genetic disorders, but rather by scientists who argued that a concerted research program was an expeditious way to improve research on all diseases. This was a subtle departure from traditional biomedical politics, in which those affected by a disorder generally lobbied for funds to stop their suffering. The rationale was still ultimately linked, and legitimately so, to preventing the suffering caused by disease. The genome project was initially presented by scientists, however, not disease-group advocates, and its impetus came from technology rather than a specific disorder. The successful launching of the genome project demonstrated that biomedical research as an enterprise could flex its political muscles.

By 1993, biomedical research consumed more than $10 billion per year in federal funding and somewhat more in private funding, mainly from pharmaceutical firms and biotechnology companies. The pharmaceutical industry alone invested $6.6 billion in 1990 and employed almost thirty thousand research and development workers.[18] Between public and private funding, there were more than 100,000 people who made their living in biomedical research, more than half deriving most of their funding from NIH—a large enough group to function as a political interest group, or minor government-dependent industry, with its eye on jobs and fiscal stability.

The explosive growth of biomedical research in the period since World War II presented a deep irony. The wealth of scientific knowledge flowing out of this public investment made it abundantly clear just how immensely difficult it would be to conquer chronic disease. President Nixon's War on Cancer, begun in 1971, was likened to the Manhattan Project. This frontal assault on a dread disease promised to produce a cure by 1976. By the 1980s and 1990s, such audacity seemed reckless. Naiveté of this magnitude is almost impossible to understand in retrospect, given the complexity of human biology. Many have come to suspect that the promises were deliberately overstated in order to extract a federal boost in research dollars, a cynical ploy undertaken by cancer research enthusiasts with full knowledge that there would never be a full accounting.

The War on Cancer had indeed succeeded in expanding biomedical research, but had not led to a cure for cancer. Instead, it helped fuel the work that led to recombinant DNA technology, DNA sequencing, and the other remarkable advances in molecular biology during the 1970s. These, in turn, spawned the new biotechnology and its industrial applications. The gnawing question was not whether good had come from the federal infusion of funds—clearly it had—but whether the scientific community had obtained it under false pretenses. Watson had called the War on Cancer "lunacy" in 1973,[19] and was careful not to promise more than he thought the genome project could actually deliver. He was quite enthusiastic about it, but did not deliberately mislead Congress. Others danced closer to the edge, but it is clear from the record and from interviews with those controlling NIH funding that Congress and budget officers in the executive branch understood the genome project to be a genetics infrastructure project. This did not alter the underlying policy problem—the difficulty of sustaining long-term government commitments.

Understanding human biological function will cost a lot of money, and will consume the careers of thousands of investigators for many generations. To approach the goals of today, biomedical research will require billions of dollars for many decades at least. Indeed, the quest will prove endless, as humans will always die of some cause. As today's scourges are eradicated or their effects softened, new diseases will rise to prominence. The twentieth century has seen an extraordinary shift in patterns of mortality. The leading causes of death in developed nations have changed from infectious disease to chronic disease. Tuberculosis, typhoid, pneumonia, polio, meningitis, smallpox, yellow fever, and other infections have given way to cancer, heart disease, stroke, and Alzheimer's disease. Medical technology has not been the only cause of this shift, which began before the antibiotic era, but technology has accelerated the trend and amplified its magnitude.

Those diseases that were most amenable to a "technical fix," through antibiotics or surgery, have been greatly reduced in incidence, prevalence, and severity, dropping several rungs on the ladder of public health problems. The future is likely to see a similar phenomenon, with those disorders that yield to

the day's scientific capacity falling first. This is not an excuse for inaction—far from it. There is plenty of suffering to relieve in families like the Rosses, or in people confronting schizophrenia, cancer, stroke, heart disease, or AIDS. The fact that humans must die of something merely means that the road is long. One of the main lessons of modern biomedical research is that science is not very far along it. One does not take a break one mile into a marathon. The inevitability of death is thus hardly an argument to reduce attention to those conditions that wreak havoc among the living. If someday it might become difficult to justify replacing one disease with another of later onset, that day is still a long way off.

At the same time that biomedical researchers have grown sufficiently in numbers to become a political interest group, their mission to eradicate disease has been complemented by a new mission to create wealth and jobs and to promote the national economy through innovation. Health care, the market for most innovations devised through biomedical research, has become an ever larger fraction of the national economy. Health expenditures rose from 5 percent of the Gross National Product just after World War II to 12.1 percent in 1991[20;21] and are projected to reach 18.1 percent of Gross Domestic Product by the year 2000 (and 32 percent by 2030).[22] Health care was grabbing a larger share of the total economy and doing so significantly faster in the United States than in any other major industrial country.[21] Were this the computer industry or automobiles, such growth would have been regarded as auspicious, the mark of an economic sector with remarkable potential for continued expansion.

Health services are highly labor-intensive, and thus a major source of new jobs, but the service components cannot be exported and the government is a major payer. Health costs are thus not only a source of jobs but also a drag on the economy; given the choice, people would rather spend their money on something else. Health expenditures do not result in possession of enduring material goods or have great entertainment value. Moreover, health goods and services are largely immune from normal market forces, particularly regarding price discipline. People are not in a position to comparison-shop or to sift through price-sensitive business calculations about when and how much health care to purchase; only a fraction of medical expenses are paid out-of-pocket, dramatically reducing price sensitivity. This reflects a deep and laudable desire not to have economic forces determine life-and-death decisions, but it plays havoc with economic rules. Expenditures in the health sector have consistently outstripped those in the rest of the U.S. economy since 1947, particularly in the 1970s and 1980s.[20;21]

Some parts of the health care industry manufacture high-value-added goods, such as pharmaceuticals and medical devices, that can be exported and sold as commodities. They are more similar to other goods in this respect than are hospital services, physician visits, or nursing homes. But they too are increas-

ingly regarded as taking undue advantage of their government-sanctioned monopoly (patent rights) to extract unseemly profits from people who depend on drugs and medical devices for their well-being, or even survival. Many controversies have erupted over drug pricing for AIDS treatments, a treatment for the rare genetic condition Gaucher's disease, and new growth-factor drugs to combat chronic kidney failure and other conditions.[18]

The cost of pharmaceuticals is a small fraction of total health expenditures, accounting for roughly 8 percent,[23] but it is a highly profitable sector. The return to pharmaceutical research and development is highly dependent on government policies—regulatory approval processes, research and development tax credits, tax subsidies for manufacture in U.S. offshore possessions such as Puerto Rico, orphan drug provisions, and payment for drugs through government health entitlement programs. Taxpayer support for the scientific and technical engine that drives much biomedical innovation—NIH research—is another major area of federal policy that directly affects the future of pharmaceuticals.

New technology growing out of biomedical research is by no means solely responsible for the cost escalation of health care expenditure, and the pharmaceutical sector accounts for only a small fraction of increased costs. Indeed, there have been clear examples of cost-saving pharmaceutical innovations, such as the reduction of iron lung use after the polio vaccine or the shortened length of hospital stays that followed the introduction of antibiotics. The advent of recombinant DNA pharmaceuticals shared some attributes of earlier innovations. Following treatment with the growth factor erythropoietin, for example, some patients with kidney failure can live who would have died in the recent past. Developing that single drug put the biotechnology firm Amgen on the pharmaceutical landscape. While pharmaceuticals made using recombinant DNA techniques may be life-saving and highly innovative, their price tends to be quite high. This is partly explained by the considerable new front-end investment in biological science, adding to the already costly process of discovering and testing a new drug.[18]

Prices for prescription drugs rose faster than general inflation and higher even than inflation in the health sector through the 1980s. Some of this increase was due to the higher cost of developing a new drug,[18] and some was due to improved quality and introductions of entirely new kinds of pharmaceuticals.[24] (This is analogous to tracking only the price of new cars, without taking into account better gas mileage, higher reliability, and safety improvements. Many new drugs, by analogy, are like cars that can traverse rivers or fly.) Despite the escalating costs of doing business, however, it appears that investments in pharmaceuticals still enjoy a higher rate of return than other industries, even when adjusted for the high risks.[18] Molecular biology has transformed the pharmaceutical industry; but the industrial applications of molecular biology are also transforming the process of biomedical research.

Biomedical science has become ever more tightly tethered to an industry,

and a highly profitable one at that. Questions about how industrial funding of university research might corrupt the pure motives and independent inquiry of science arose even as the biotechnology revolution began in the late 1970s, when the magnitude of such investment was relatively low. By 1993, the Office of Technology Assessment, in discussing this policy issue, concluded that the evidence appeared to indicate that those few scientists with substantial industrial funding agreements published more and taught more, and so "commitment to the academic institution appears not to be a big problem"; the potential for conflicts of interest arises in only "a very small minority of cases."[18] While conflict of interest for individual investigators might not often conflict with science, the ethos of publicly funded academic research nonetheless confronted deep systemic problems.

The 1980s clearly brought a dramatic shift in the role of biomedical research, and yet public perceptions and public policy have not yet adjusted. Federal policies on technology transfer are contradictory. One faction of Congress promotes industrial applications of research, while others are deeply suspicious of industrial ties. Both pristine science and vigorous technology transfer are laudable goals, but they come into conflict from time to time.

A string of laws, beginning in 1980, gave patent rights to universities doing research, but universities are now beginning to make agreements with corporations that could result in taxpayers giving hefty research subsidies to private firms. For a few tens of millions of dollars, a company might wrap up the patent rights to university work paid for by federal grants, thus leveraging a public research investment many times larger than the private one. The main beneficiaries may be the universities or research centers and the investigators. This promises to emerge as a major issue in the 1990s.

The decade that culminated with the human genome project also saw a powerful alignment between biomedical research, commercial biotechnology, and pharmaceutical innovation. Much good can come from this synergy, but promotion of biotechnology must inevitably collide with the other public policy goal of constraining how much health care encroaches on the rest of the economy. Moreover, the public is likely, slowly but ineluctably, to become more suspicious of biomedical research that is financially rewarding as well as a purely academic pursuit aimed at mitigating suffering.

The public is sure to sense the emerging power of a research-industrial complex that is growing in size, much as the military-industrial complex that President Eisenhower warned of in the late 1950s. The question is whether biomedical scientists, and genome researchers in particular, can keep their hands clean in an environment that consumes more and more resources, relentlessly increases in scope and scale, and depends on the federal government for succor.[25;26] Research funded by private foundations, by other philanthropies, or from venture capital is far less at issue than research that taxpayers fund. Private funding sources must make difficult decisions about the purposes

of their research, how to allocate patent rights, how much their funds can be used to support industrially relevant research, and when to share data. Unlike federally funded research, however, this is a private matter rather than a public policy problem.

The values that have merged science as the dispassionate pursuit of truth with the profit motive are a volatile mix. Early critics worried that the inflated rhetoric supporting the genome project was due to the personal aspirations of its promoters. How much more weight might their concerns have carried had there also been financial motives? The monetary rewards of genome research are becoming more apparent. The genome project is destined to be a proving ground for the new rules governing science.

The future of the genome project will clearly be caught up in an abstruse technology-transfer debate about the industrial uses of its information, but the broad social impact of genome research will depend on the degree to which it can recast the debate about genetic determinism. The twentieth century began with the emergence of genetics as a science, and quickly got caught in a simplistic interpretation of inheritance that bred the eugenics and racial hygiene movements. These were virulent ideologies that provoked a backlash, casting a long shadow over the science itself. Both genetic determinism and its equally flawed antagonist, environmental determinism, are utterly incapable of explaining biology. As genetics turns up more and more knowledge about the role of genes in diseases and other traits, will the same simple-minded interpretations of genetics continue to dominate public discourse? Will "it's genetic" continue to mean "we can't do anything about it" in cocktail party prattle? Will genetics continue as the stalking horse for racist ideology and ethnic prejudice? Surely we can move beyond these vacuous ideologies to a richer understanding that embraces both genetic and environmental factors in the complex dance of life. The interesting question is not whether it is nature or nurture, but how they interact.

In the 1970s, molecular biologists imposed a moratorium on themselves while they debated the safety of recombinant DNA research. Historical interpretations differ on whether it was science or self-interest that played the leading role in ending the moratorium,[27–29] but the fact that the moratorium took place and was self-imposed is not in question. This gives molecular biology a social cast unlike the secrecy of the Manhattan Project. The birth of the research program on ethical, legal, and social issues (ELSI) follows this precedent in a new form, attending explicitly to the social impact of science. One of the most daunting tasks of the ELSI program is to change the social framework in which genetics is cast. The public debate need not repeat historical mistakes premised on genetic determinism or cling to a reactive environmental dogmatism. How genes influence biology and behavior is an extremely complex phenomenon that science has only begun to understand. Immense beauty

resides in understanding it; immense joy in finding it out. At its best, genome research can replace caricature with nuance, and provide a richer vocabulary for understanding genetics.

In the end, nations must decide how to spend their public dollars. Biomedical research is a public good, and the genome project is intended to make that research go faster and probe deeper. Is this more or less important than a new highway? New weapons? Health care? Social Security? In the grand scheme of things, the answers to such questions return to the lives of citizens. The Ross family lives with Alzheimer's disease every day, but it also enjoys movies and protection by the armed forces. How much is it worth to them to get rid of Alzheimer's disease? The answer is clearly a lot, but not everything. Most families can find a similar dread disease somewhere in their pedigree. Producing new knowledge through the discipline of science, building on the work of others towards a universally laudable goal, is a noble pursuit—or at least it can be. Few jobs can be more gratifying than discovery. A biomedical researcher lays small bricks in a growing edifice, but one whose foundation is far more stable than those of most other professions. If it can preserve its noble aims and promote social policies to thwart the demonstrably destructive power of genetic information, the genome project can build a permanent monument of new knowledge—a solid structure of great beauty but also immense practical significance. Understanding ourselves better can benefit everyone.