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Foreword

Donald Fredrickson's memoir provides a unique perspective on the recombinant DNA debate in the United States, especially during the years 1975 through 1981. As director of the National Institutes of Health (NIH), his perspective was that of the leading executive-branch policymaker for recombinant DNA research during this period. In the following pages we see the diverse roles played by the NIH director, other scientists, members of Congress, the Secretary of the U.S. Department of Health, Education and Welfare, multiple federal agencies, business leaders, experts in law and ethics, public-interest advocates, and members of the general public. In addition to mediating among these domestic individuals and groups, the NIH director found it necessary to remain in touch with scientific peers in other nations. The scientific and political leaders of all industrialized countries were wrestling with their responses to this exciting but potentially hazardous new type of research.

The central section of the book (chapters 1 through 10) focuses on one 3½-day meeting, the Asilomar Conference held in February of 1975, and one group that carried forward the work of the Asilomar meeting, the NIH Recombinant DNA Advisory Committee (RAC). This meeting and this group should be considered together because each complemented the other. The conference reached a consensus on reasonable initial rules for conducting recombinant DNA research (and for deferring certain kinds of experiments), while the RAC continued the work of Asilomar, refining the initial guidelines and revising them in the light of further research.

From my perspective as a three-term member of the RAC, the Asilomar meeting was an important and highly constructive endeavor. At the meeting, leading members of the scientific community sought to assess the potential

hazards of the research they were planning to conduct. One can quibble about details of the meeting—for example, the narrowness of the invitation list and the meeting's semi-private character. However, in examining the trees one should not lose sight of the forest. An 18-month process of discussion and deliberation, led by Maxine Singer and Paul Berg among others, culminated in an international scientific summit. At the summit a provisional consensus was reached about the most prudent course for the early years of recombinant DNA research. The planners of the summit meeting also proposed that an ongoing advisory committee be created to oversee future research in the field.

For its part, the RAC met for the first time immediately after the Asilomar meeting and devoted its first year to developing an initial set of "Guidelines for Recombinant DNA Molecule Research." After a public review of the draft guidelines, in which I was privileged to take part, they were published in July 1976. During the next 2½ years an increasingly interdisciplinary RAC struggled to revise the 1976 Guidelines in the light of data emerging from the conduct of the research. Meanwhile, legislators in the United States Congress and in some municipalities considered whether the RAC and its NIH-based staff were sufficient to oversee the rapidly expanding field of recombinant DNA research. In the end, a new social compact was implicitly adopted, and, beginning in 1979, an expanded RAC that represented a wider variety of perspectives was permitted to continue as the central oversight body. By about 1982 the task foreseen for the RAC at Asilomar had been essentially completed, and the few vestiges of oversight that remained had been delegated to local institutions.

Did scientists like Maxine Singer and Paul Berg make a mistake in calling attention to the potential hazards of laboratory research with recombinant DNA? With the benefit of hindsight, one can argue that recombinant DNA research turned out not to pose unique dangers. However, the knowledge that was available to the scientific community in 1973 or 1975 gave no firm basis for estimating the harms that this new type of research might cause to laboratory workers or the environment. The potential hazards to laboratory workers of research with infectious microbes and oncogenic viruses were well known, as were the risks of research involving radiation or toxic chemicals. Thus, careful thought and interdisciplinary deliberation before proceeding with at least certain types of experiments seems, even today, to have been a prudent course. In addition, the scientific community's willingness to raise safety questions in the absence of any demonstrated harm enhanced public confidence that in the future scientists also would level

with the public in discussing the potential benefits and harms of new lines of research. (This thoughtful warning mode contrasts starkly with the overly optimistic reassurances that the public was given about the purity of the blood supply during the early years of the AIDS epidemic, or about the safety of eating beef despite increasing evidence that mad cow disease was somehow being transmitted from cattle to humans.)

Were the early research guidelines that emerged from Asilomar and the RAC too conservative, too stringent? Again, hindsight increases confidence. By the beginning of 1979 even one of the earliest proponents of caution, Maxine Singer, was expressing concern that the Guidelines were not being relaxed quickly enough and that the RAC was beginning to resemble a "ponderous" regulatory agency.[1] However, the major problem in the years 1976 to 1978 may not have been the initial conservatism of the Guidelines as much as it was the lack of a clearly articulated process for their timely revision. Because of this oversight in the 1976 Guidelines, proposals for revision themselves may have seemed like potential violations of an unchanging (or unchangeable) code. An activist Secretary of Health, Education and Welfare and members of Congress who seemed ready to create a new regulatory agency may also have slowed the revision process. However, the delays of 1978 and 1980 gave way to a rapid relaxation of the Guidelines in the early 1980s, and oversight policies in multiple industrialized countries seem to have been relaxed roughly in parallel. In toto, recombinant DNA research is not likely to have been set back by more than 2 or 3 years at the most by Asilomar and the RAC, and the caution that caused this delay was, at least in part, arguably a prudent response to reasonable concerns about possible biohazards.

Was NIH the most appropriate agency for overseeing laboratory research with recombinant DNA in the late 1970s? While there are theoretical advantages to separating the distinct functions of funding research, on the one hand, and providing oversight for research, on the other, the ad hoc arrangement suggested by the planners of the Asilomar meeting seems to have worked reasonably well for recombinant DNA research. Several factors may have contributed to the apparent success of this arrangement. First, most funding for recombinant DNA research in the 1970s was federal, with the lion's share being contributed by NIH and the National Science Foundation. Thus, a uniform set of federal research guidelines was likely to be adhered to by researchers who knew that failure to act in accordance with the NIH Guidelines could jeopardize their research funding. Second, the NIH Office of Recombinant DNA Activities (ORDA) and the RAC were

transparent in all of their early actions, meeting in public and publishing large volumes of material in a public record. Third, the NIH director was strongly supportive of the RAC, meeting with the committee regularly to brief RAC members on recent research developments or his thinking about their role; at the same time, he allowed the committee complete independence in its work. Fourth, in response to gentle prodding by the Secretary of Health, Education and Welfare, the NIH director expanded and diversified the membership of the RAC in late 1978. With this expansion the RAC came to be seen as broadly representative of the spectrum of public opinion on recombinant DNA research. Finally, the staff members at ORDA were dedicated public servants, and most RAC members took their oversight responsibilities very seriously.

The last three chapters of this memoir (chapters 11 through 13) cover scientific and public policy developments in 1980 and early 1981, as well as providing the author's overall perspective on the recombinant DNA research controversy. During this time the RAC took on a quasi-regulatory role vis-à-vis the private sector, formulating guidance on safety standards for large-scale production using recombinant DNA techniques and reviewing proposals voluntarily submitted by companies like Genentech and Eli Lilly. For the first time, RAC members were confronted with decisions about whether to go into executive session to review information that companies wished to maintain as proprietary. As NIH director, Don Fredrickson encouraged RAC members to accept this role for the public good until other agencies—in this case, the Food and Drug Administration (FDA)—could develop their own oversight capabilities. In retrospect, Dr. Fredrickson expresses satisfaction that the RAC helped to prevent delays in the transition from the laboratory to the manufacturing plant.

The year 1980 was critical for the RAC and NIH in another way. Martin Cline of UCLA conducted an unauthorized attempt to use recombinant DNA techniques to treat two patients, one in Israel and one in Italy, who were afflicted with thalassemia.[2] Rather than asking the RAC to perform an investigative and judicial role, the NIH director appointed an ad hoc committee composed of NIH employees. When the investigation verified that both the "Guidelines for Recombinant DNA Research" and federal regulations for the protection of human subjects had been violated by Dr. Cline, Don Fredrickson did not hesitate to impose the rather harsh penalties recommended by the ad hoc committee. Dr. Cline's current NIH grants were affected, as was his ability to secure new NIH grants during the following 3 years.

In 1980 and 1981 the NIH director and the RAC itself also confronted serious proposals to abolish the RAC and its supporting organization, ORDA, and to transform the remaining mandatory Guidelines into a voluntary code of practice. Among the proponents of these changes were some of the organizers of the Asilomar Conference, who 7 years earlier had urged caution in research with recombinant DNA and had strongly supported the creation of the RAC. Don Fredrickson and the new RAC Chair, former Congressman Ray Thornton, advocated and indeed implemented a more moderate approach: further relaxation of the Guidelines and the retention of the RAC as an oversight body that could provide expert advice to the scientific community and that would simultaneously reassure the public and policymakers. In this connection, the NIH director proposed another metamorphosis for the RAC, into a "third-generation" body. The first-generation RAC had been predominantly scientific and had relied on the more broadly constituted NIH Director's Advisory Committee (DAC) for additional perspective. In contrast, the second-generation RAC of late 1978 and 1979 included both scientific and socially oriented viewpoints within the RAC itself. In 1982, shortly after leaving the directorship of NIH, Don Fredrickson called for another transition in the role of the RAC, into an even more inclusive body that would be "better equipped to deal with the emerging problems" while simultaneously being "relieved of some of the detailed burden of reviewing minor administrative concerns."[3]

The next transformation of the RAC took place shortly after this proposal, but the change occurred in response to a report by a presidential advisory commission on bioethics and a new turn in biomedical research—the use of recombinant DNA techniques for human gene transfer (also called "human gene therapy"). In November of 1982 the President's Commission on Bioethics released a report entitled *Splicing Life*.[4] The commission's report sought to de-dramatize the dangers posed by "human genetic engineering" by pointing to similarities between gene transfer for therapeutic reasons, on the one hand, and traditional drugs and biologics, on the other. In the final chapter of its report, the President's Commission also discussed alternative oversight strategies for the emerging field of human gene transfer research. One of three options considered by the commission was the possibility of "revising RAC," adapting its goals and membership to prepare the committee for the new task at hand. In this connection, the commission explicitly referred to Don Fredrickson's notion of creating a "third-generation RAC."[5]

During the next 2 years, under the leadership of a new chair, Robert Mitchell, the RAC considered whether it should accept responsibility for

reviewing human gene transfer protocols on a case-by-case basis. In incremental steps RAC members accepted this responsibility in principle, then created a Working Group (later Subcommittee) on Human Gene Therapy to perform the initial review of protocols on the RAC's behalf. In late 1984 and the first half of 1985 this working group developed a set of guidelines called "The Points to Consider"[6] that served as the framework for evaluating human gene transfer protocols. I had the privilege of chairing the working group during the 7 years of its existence.

In the Epilogue to his memoir (chapter 13), Don Fredrickson recounts several important moments in this new phase of the RAC's activity. He briefly reports on the first authorized human gene transfer experiment, which was performed at NIH in 1990 by R. Michael Blaese, W. French Anderson, and their colleagues. He also acknowledges the FDA's acquisition of formidable expertise in cell and gene therapy in the early 1990s but notes that the RAC review process for gene-transfer protocols was a matter of public record, while FDA's reviews of Investigational New Drug (IND) applications occur behind closed doors. With a trace of sadness the author reviews the attempt by NIH director Harold Varmus to abolish the RAC in 1996 and the opposition to the proposed abolition that was expressed by a variety of individuals and groups, including the American Society for Microbiology, "the largest single life science society in the world."[7] With regret Don Fredrickson carries his account forward to 1999 and to the death of Jesse Gelsinger, a relatively healthy participant in a University of Pennsylvania protocol focused on ornithine transcarbamylase (OTC) deficiency. He comments that, in the wake of this subject's death, new and more stringent rules for all research with human subjects are likely to be enacted—especially regarding researchers' financial involvement in the research they are conducting.

Dr. Fredrickson's reference to the financial dimension of biomedical research reminds us quite forcefully of the major changes in the context of this research that occurred between 1975 and 2000, to choose two convenient dates. These breathtaking changes are reflected at several points in this memoir. For example, in 1976, Don Fredrickson notes, there was "the patent"—the Boyer-Cohen patent, held by Stanford University and the University of California on one of the major techniques for combining DNA from different organisms. He notes that this patent was governed by one of 167 Institutional Patent Agreements (IPAs) that had been reached between the Department of Health, Education and Welfare and universities.[8] Under the terms of an IPA, a university could grant an exclusive license to

a third party only if it could demonstrate that a nonexclusive license was infeasible. Further, the IPA stipulated that the federal government must be granted a license for use of an invention for research purposes at no cost. While acknowledging the importance of private enterprise for translating researching findings into useful products, Don Fredrickson notes somewhat ruefully that the *Diamond v. Chakrabarty* decision by the U.S. Supreme Court (1980) and the Bayh-Dole Act of 1980 have contributed in major ways to a paradigm shift in biomedical research. Today most innovations in biomedical research, including genes, are aggressively patented by both private companies and academic institutions. Quite clearly the author is concerned that the pendulum may have swung too far in the entrepreneurial direction, to the detriment of basic science.[9]

The sources of funding for biomedical research and development have changed radically since the 1970s, as Don Fredrickson's narrative suggests. According to figures compiled by the NIH, federal expenditures for medical and health-related research and development nearly doubled from $6.8 billion to $13.4 billion between 1986 and 1995.[10] During the same period, industry expenditures for biomedical and health-related research more than tripled, growing from $6.2 billion in 1986 to $18.6 billion.[11] In one part of industry, the segment represented by pharmaceutical companies, the rate of growth in research and development expenditures has been even more dramatic. According to the industry's trade association, PhRMA, pharmaceutical company investments in this sphere have increased from $1.5 billion in 1980—the year of the Cline experiment—to $22.4 billion in 2000.[12]

Is there a role for the RAC and other RAC-like oversight bodies in this new era when private investment in biomedical research and development will clearly outstrip public funding? Or would it be better to have all oversight of this research focused in regulatory agencies, in particular, the FDA? One's answer to these questions will depend largely on one's overall regulatory and political philosophy. If the primary goal of biomedical research and development is to speed useful products to the market and to preserve one nation's competitive position in the global economy, then minimal regulation and a tilt toward approval would seem to be the appropriate regulatory stance. However, if one considers the informing of the public about new biomedical developments and the protection of human subjects in clinical trials to be equally important goals, then a more transparent and inclusive oversight system may be required. From my perspective, the RAC in its early years of overseeing recombinant DNA research and human gene transfer research provides an excellent model for the responsible introduc-

tion of a new technology. Again, in my own view, this model is eminently applicable to other emerging fields of biomedical research, for example, xenotransplantation. Where the RAC and parallel advisory committees should be located within the structure of the federal government is, of course, a different question. In the future, there are at least good theoretical arguments for separating the oversight of research from its funding and for stipulating that the RAC and similar bodies should report to a Cabinet secretary or even to an independent agency dedicated to the promotion of ethically responsible research.[13]

One of the most striking statements in Don Fredrickson's memoir appears in chapter 4. There he comments, "Although the directorship of NIH was itself a full-time job, I estimated later that I had to devote at least half of my time to recombinant DNA during 1976–78."[14] This level of commitment to an exciting but potentially hazardous field of research was by no means required of the NIH director. Prior and later directors of NIH would undoubtedly have handled the circumstances of 1976 differently, perhaps deferring to the will of Congress, to the political instincts of the Secretary of Health, Education and Welfare, or to the regulatory authority of the FDA or the EPA. Instead, Don Fredrickson immersed himself in the day-to-day activities required to protect scientific freedom—a freedom that was, from the beginning and almost without exception, exercised in a socially responsible manner. He also nurtured a fledgling advisory committee, the RAC, maintaining regular communication with its members and helping the committee to adapt to changing scientific and social circumstances.

The payoff from this investment of time and energy, both within the United States and in the scientific community around the world, was enormous. Recombinant DNA research techniques were introduced into the world's laboratories in a thoughtful, cautious, and ultimately innocuous way in full view of the public and public policymakers. We owe a great debt of gratitude to the author of this book both for his dedicated public service during those critical months and years and for this vivid account of the major steps in the policy-making process.

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Preface

I remember the Asilomar Conference as an event both exciting and confusing. Exciting because of the scale of the scientific adventure, the great expanses which had opened to research, and because no one could be indifferent to the debate over the powers and responsibilities of scientists. Confusing because some of the basic questions could only be dealt with in great disorder, or not confronted at all. On the frontiers of the unknown, the analysis of benefits and hazards was locked up in concentric circles of ignorance . . . how could one determine the reality . . . without experimenting . . . without taking a minimum of risk?[1]

PHILIPPE KOURILSKY

The controversy over recombinant DNA broke out suddenly over 30 years ago, when it was discovered that genes from different species of bacteria could be recombined in the laboratory. Fear of the potential hazards quickly grew, and in 1974 a small group of American academic molecular biologists called for a worldwide moratorium on such experiments until the risks could be assessed. In February 1975, 150 scientists from the world's premier laboratories convened for three days at Asilomar Conference Center in Pacific Grove, Calif., to study the problem and formulate an approach to its solution. The conference voted to replace the moratorium with a complicated scheme of rules for containment and restriction of research, which severely limited experimentation and paradoxically hobbled determination of the actual risks. Prior to Asilomar, the conference organizers, led by Paul Berg, had also requested that the National Institutes of Health (NIH) establish guidelines for all research with recombinant DNA.

On the 25th anniversary of Asilomar, in February 2000, I visited the conference site for the first time. In the company of many scientists who had earlier been conferees, I walked along the beach, poked my head into the chapel, and listened to the luncheon bell which had ended that first gathering so long ago. For me there was a special meaning in the occasion, for I had just completed this memoir of how the Asilomar meeting had touched my scientific career, setting the daily calendar and demanding my every attention for six eventful years. I became the director of NIH in July 1975 and unsuspectingly inherited the job of guiding the recombinant DNA

controversy through its first exciting, tormented years. The issuance, evolution, and adaptation of the *NIH Guidelines for Recombinant DNA Research* became the focus of more than a decade of suspicion of this audacious new science. This book attempts to describe the actions which NIH and a new Recombinant DNA Advisory Committee (the RAC)—under the careful watch of the scientific community, the government, and skeptical members of the public—undertook to win society's acceptance of this new technology while keeping the science moving cautiously forward.

When the lay public realized the extent of the strange new dangers discussed at Asilomar, the tolerance of many critics suddenly took a turn for the worse. Laymen, scientists, and legislators, on one side or the other, engaged in an angry struggle over the resumption of research and the rules *established by scientists* to control it. Some prominent scientists warned that the new power to join pieces of genes from different sources would create chimeric products that could seed into niches in the environment and possibly spread new diseases beyond control. As expected, and as it should, society reacted. Many hearings, demonstrations, forums, and town meetings were held. In townships, state legislatures, and the U.S. Congress, bills to govern laboratory research were drafted and debated at length. Injunctions to forbid all such experimentation were sought in the courts. More than half a decade of recriminations and anxiety passed before society and biomedical science gingerly patched up the largest rents in their mutually beneficial entente.

Why did this happen? Could it have been avoided? Can we be sure that such a threat to a relationship necessary for the advancement of our civilization will not happen again?

The purpose of this memoir is not to re-tell the story of Asilomar, but to place in context all that subsequently happened. Because I inherited principal responsibility for the *NIH Guidelines for Recombinant DNA Research* that grew from the Asilomar meeting, I became the federal officer answerable for protection of the public welfare as well as the furtherance of the scientific research that had come abruptly to a halt. As such I was the principal spokesman in Congress, and the focal point of attention of the secretary and the hierarchy of the Department of Health, Education and Welfare, on all matters of fear and uncertainty created by recombinant DNA.

Most of what all of us did in that atmosphere of crisis to fulfill our public duties and to preserve the nation's capacity for preeminence in biomedical research has never been published. Thus our successes and our errors have

been unavailable for such instruction as they might hold of how best, in the future, to help preserve intact the interface between high science and a powerful government. I attempt here to lay out the roots of that vital relationship as it involved NIH, the nation's single most important biomedical research agency.

Fortunately, great pains were taken to maintain from the beginning most of the vast archives of hearings records, correspondence, and documents relative to our actions.[2] In addition, I preserved a thorough record of my own activity, including extensive diaries covering this period. Across the pages of this memoir move numerous personalities from microbiology, molecular biology, and other scientific disciplines, as well as the leaders among Congress, the administration, and government agencies, environmentalists, and many others who had a role at this time of testing.

At the moment of the Asilomar meeting, the modern world was entering a phase of transition, evolving toward a society in which the once arcane discipline of molecular biology was swiftly becoming a significant force in medicine, commerce, ethics, sociology, politics, and the very nature of science itself. The initial phase of this transition was taken up with determining how dangerous was the new technology and informing the public of every step by a totally open process.

With the booming development of a whole new culture of genomics and medicine, the early fears of physical danger have disappeared, to be succeeded by new controversies—many involving serious moral and ethical issues. The basic scientists, their government sponsorship—joined now by commerce—and the public are striving to preserve a workable social contract. This book describes in detail the earliest of such endeavors, a serious and prolonged struggle that set the stage for more extraordinary times to come.

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