

Appendix III-A

History of the Recombinant DNA Debate

The history of the debate over the risks from rDNA techniques and the Government's response may be divided into four phases. * Phase I covered the period from the first awareness of risks to human health from experiments involving recombinant DNA (rDNA) in the summer of 1971 to the end of the Conference at the Asilomar Center in February 1975, which resulted in prototype guidelines covering the research, Phase II covered the period from Asilomar through the development by the National Institutes of Health (NIH) of the Guidelines of June 1976. In this period, the public first became significantly involved in the debate and most, if not all, of the policy issues were clearly framed. Phase III, from mid-1976 through mid-1978, involved congressional consideration of the issues in an atmosphere that went from almost imminent passage of legislation to the cessation of such efforts. Phase IV covers the postlegislative period, when NIH and its organizational parent, the Department of Health, Education, and Welfare (HEW) (now the Department of Health and Human Services) undertook to develop satisfactory voluntary standards in areas over which they had no legal authority and to accommodate growing pressure for public involvement, while avoiding a full regulatory role.

Phase I began in the summer of 1971, when several scientists became concerned about the safety of a proposed experiment to insert DNA from SV40 virus, a monkey tumor virus that also transforms human cells into tumor-like cells, into a type of bacteria naturally found in the human intestine. After months of discussion, the scientist who had proposed the experiment decided to defer it. Meanwhile, as rDNA techniques became more refined, debates about safety increased; at the June 1973 Gordon Research Conference, safety issues were discussed. The participants voted: to send a letter to the National Academy of Sciences (NAS) and the National In-

stitute of Medicine requesting the appointment of committees to study potential hazards to laboratory workers and the public; and by a narrow majority⁴ to arrange for the letter to be published in the widely read journal, *Science*, to alert the broader scientific community.⁵

NAS appointed a committee of prominent scientists involved in rDNA research. In July 1974, the panel asked for a temporary worldwide moratorium on certain types of experiments, and called for an international conference on potential biohazards of the research through a letter published in *Science* and its British counterpart, *Nature*.⁶ This letter also requested the Director of NIH to consider establishing an advisory committee to develop an experimental program to evaluate potential hazards and establish guidelines for experimenters.

In response, the Director of NIH, after authorization by the Secretary of HEW, established the Recombinant DNA Molecule Program Advisory Committee (later renamed the Recombinant DNA Advisory Committee, RAC) on October 7, 1974, along the lines suggested by the NAS Committee. The Committee's charter described its purpose as:⁷

The goal of the Committee is to investigate the current state of knowledge and technology regarding DNA recombinant, their survival in nature, and transferability to other organisms; to recommend programs of research to assess the possibility of spread of specific DNA recombinant and the possible hazards to public health and to the environment; and to recommend guidelines on the basis of the research results. This Committee is a technical committee, established to look at a specific problem. (Emphasis added.)

The international conference called for by the NAS Committee letter was held at the Asilomar Conference Center, Pacific Grove, Calif., in February 1975. The organizing committee made it clear that its purpose was to focus on scientific issues rather than to become involved in considering ethical and moral questions. However, in one session the few lawyers

¹For a detailed history through 1977, see footnote 1. For a history and a discussion of the broader issues, see footnotes 2 and 3.

⁴Swazey J. Sorenson, and C. Wong, "Risks and Benefits, Rights and Responsibilities: A History of the Recombinant DNA Research Controversy," *Southern California Law Review* 51:1019 (September 1978).

⁵C. Crabtree, *A Double Image of the Double Helix* (San Francisco: W. H. Freeman Co., 1979).

⁶D. Jackson, and S. Sorenson (eds.), *The Recombinant DNA Debate* (Englewood Cliffs, N. J.: Prentice-Hall, Inc., 1979).

⁴Swazey et al., *op. cit.*, p. 1,023.

⁵Letter from Maxine Singer and Dieter Soil to the National Academy of Sciences (NAS) and the National Institute of Medicine, reprinted in *Science*, vol. 181, 1973, p. 1114.

⁶Letter from Paul Berg, et al. to the editor, reprinted in *Science*, vol. 185, 1974, p. 303.

⁷The charter of the Recombinant DNA Molecule Program Advisory Committee, Oct. 7, 1974.

invited confronted the scientists with some of these questions.' The conference report concluded that although a moratorium should continue on some experiments, most work involving rDNA could continue with appropriate safeguards in the form of physical and biological containment,

In *Phase II*, the debate widened to encompass broader social and ethical issues, such as the relationship between scientific freedom of inquiry and the protection of society's interests, in whatever manner those were defined. Such issues led naturally to questions about who makes the decisions and the role of the public in that process. Finally, decisionmaking mechanisms were developed. Issues raised and actions taken during this phase in many respects controlled the subsequent development of the Federal response to the debate, and created problems that continue to the present. At this stage, participation in the debate went beyond the scientific community.

Questions of ethics and public policy had been raised earlier, but they now received much wider attention. On April 22, 1975, Sen. Edward M. Kennedy, Chairman of the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, held a half-day hearing on science policy issues arising from rDNA research. In May 1975, a 2-day conference on "Ethical and Scientific Issues Posed by Human Uses of Molecular Genetics" was held under the joint sponsorship of the New York Academy of Sciences and the Institute of Society, Ethics, and the Life Sciences. In addition to molecular biologists, participants included lawyers, sociologists, psychiatrists, and philosophers.

The issue of public participation arose as decision-making mechanisms were developed. RAC was originally composed of 12 members from "the fields of molecular biology, virology, genetics and microbiology."⁹ Critics first noted the need for more expertise in the fields of epidemiology and infectious diseases, since most molecular biologists were trained as chemists. * RAC's membership was increased to 16 and the range of expertise was widened to include the fields of epidemiology, infectious diseases, and the biology of enteric organisms, by amendment to the charter on April 25, 1975.

Since some members were conducting the research in question, critics claimed that a conflict of interests existed. They also noted that the Committee

Swazey, et al., op. cit., p. 1,034.

The charter of the Recombinant DNA Molecule Program Advisory Committee, Oct. 7, 1974, op. cit.

● One of the members of the original AC (Stanley Alkow) did have substantial expertise with enteric organisms and *E. coli* in particular.

advised the Director of NIH, an agency whose mission was to foster biomedical research, not to stop or otherwise regulate it. These issues were brought out in a petition to NIH signed by 48 biologists in August 1975. Criticizing a proposed draft of the guidelines as setting substantially lower safety standards than those accepted at Asilomar, the petition argued for broader representation on RAC from other fields of scientific expertise and from the public-at-large. RAC itself had been sensitive to these limitations; in the summer of 1975, an attempt was made to recruit nonscientists.¹⁰ One nonscientist was added in January 1976, and another was added in August 1976.

In December 1975, RAC submitted revised draft guidelines to the Director of NIH, Dr. Donald Fredrickson. Although they were stricter than those drafted at Asilomar, some criticized them as being "tailored to fit particular experiments that are already on the drawing boards."¹¹ The consensus of RAC, on the other hand, was that the guidelines were excessively strict, but that it was necessary to be overly cautious because of its limited expertise in public health.¹² In any event, Dr. Fredrickson arranged for public hearings on the proposed guidelines at a 2-day meeting in February 1976 of the Advisory Committee to the Director, a diverse group of scientists, physicians, lawyers, philosopher) and others. A similarly diverse group of scientists and public interest advocates were invited to attend. Some modifications to the Guidelines proposed by Dr. Fredrickson as a result of that meeting were adopted and others were rejected by RAC in April 1976.¹³

The final major issue arising during this period concerned NIH's lack of authority to set conditions on research funded by other Federal agencies or by the private sector. In a June 2, 1976, meeting between Dr. Fredrickson and some 30 representatives of industry, including pharmaceutical and chemical companies, it became clear that some rDNA research was being done; however, the representatives appeared hesitant to commit themselves to voluntary compliance with the proposed guidelines.¹⁴ The pri-

Dr. Elizabeth Kutter, a former AC member, personal communication (Sept. 11, 1980).

10. Wade, "Recombinant DNA: Ethical Constraints Launch New Technology," *Science*, vol. 190, 1975, pp. 1175, 1179.

Kutter, op. cit.

11. *Ibid.*

12. Subcommittee on Science, Research and Technology of the House Committee on Science and Technology, Genetic Engineering, Human Genetics, and Cell Biology: DNA Recombinant Molecule Research (HDD. R Report 11) 94th Cong., 2d sess., 1976, p. 51.

mary reason was their concern over protection of proprietary information.¹⁵

Phase 11 culminated with the promulgation on June 23, 1976, of the Guidelines for Research Involving Recombinant DNA Molecules ("1976 Guidelines") covering institutions and individuals receiving NIH funds for this research.

Phase III was characterized by attempts to remedy the limited applicability of the Guidelines. Soon after their publication, Senators Kennedy and Javits sent a letter to President Ford, calling his attention to the Guidelines. They noted that any risk was not limited to federally funded research, and urged him to take necessary steps to implement the Guidelines throughout the research community. In October 1976, the Secretary of HEW, with the approval of the President, formed the Federal Interagency Advisory Committee under the chairmanship of the Director of NIH to determine the extent to which the Guidelines could be applied to all research and to recommend necessary executive or legislative actions to ensure compliance.¹⁶ In March 1977, the Committee concluded that existing Federal law would not permit the regulation of all rDNA research in the United States to the extent deemed necessary;¹⁷ it further recommended new legislation, specifying the elements of that legislation, is

During 1977, several bills to deal with this and other problems were introduced in Congress. They addressed in different ways the issues of the extent of regulatory coverage, the mechanisms for regulation, and Federal preemption of State and local regulation. The major bills were those of Rep. Paul Rogers, H.R. 7897 (and its substitute, H.R. 11192) and of Sen. Edward Kennedy, S. 1217. *

While hearings were being held, three developments occurred which, by the end of 1977, had dissipated much of the impetus for legislation. The first was the expanded role of RAC. On September 24, 1976, its charter had been amended once more to provide for additional expertise in the areas of botany, plant pathology, and tissue culture. Moreover, its membership was increased from 16 to 20 so that four members would be "from other disciplines or representatives of the general public." This was the first official provision for public representation

¹⁵Ibid., pp. 52.

¹⁶Interim Report of the Federal Interagency Committee On Recombinant DNA Research: Suggested Elements for Legislation, Mar. 15, 1977, pp. 3-

¹⁷Ibid., pp. 9-10.

¹⁸Ibid. pp. 11-1.

● For a more complete discussion of the legislation, see footnote 19.

¹⁹"Recombinant DNA Molecule Research," Congressional Research Service, issue brief No. 77024, update of Jan. 2, 1979.

although two nonscientists were already members. The number of nonscientists remained the same until December 1978.²⁰ Also, RAC's responsibilities were defined in greater detail, including the responsibility for reviewing large-scale experiments. Nevertheless, RAC continued formally at least to be "a technical committee, established to look at a specific problem."

The second development was a growing belief among scientists that the risks of the research were less than originally feared. This was based on the following: 1) a letter from Roy Curtiss at the University of Alabama to the Director of NIH, explaining risk assessment experiments using *Escherichia coli*, from which he concluded that the use of *E. coli* K-12 host-vectors posed no danger to humans; 2) the conclusions of a committee of experts in infectious diseases assembled by NIH in June 1977 in Falmouth, Mass., that the alleged hazards of the research were unsubstantiated; and 3) a prepublication report on experiments showing that genetic recombination occurs naturally between lower and higher life forms, and suggesting that the rDNA technique was not as novel as presumed.

The third development affecting the legislation was a concerted lobbying effort by scientists against what they considered to be some of the overly restrictive provisions of the bills, especially S. 1217.^{21 22 23} The efforts included wide circulation of reports (including some in draft form) as soon as available, which supported the conclusion that the research was less hazardous than originally supposed.

By the end of 1977, the legislation was in limbo. This situation continued in early 1978, although some hearings were held. On June 1, 1978, Senators Kennedy, Javits, Nelson, Stevenson, Williams, and Schweiker addressed a letter to HEW Secretary Joseph Califano, which acknowledged the likelihood that legislation would not pass and urged that deficiencies in the regulatory system be addressed through executive action based on existing authority, if that were to be the case.

During Phase IV, NIH and its parent organization, HEW (now DHHS), have attempted to operate in the regulatory vacuum left by the lack of legislation. In response to the consensus that developed in 1977 on

²⁰William Gartlan, Director of the Office of Recombinant DNA Activities, NIH personal communication, June 19, 1980.

²¹L. Cullitor, "Recombinant DNA Bills Derailed: Congress Still Trying to Pass Law," *Science*, vol. 199, Jan. 20, 1978, pp. 274-277.

²²I. Dickson, "Friends of DNA Fight Back," *Nature*, vol. 272, April 1978, pp. 664-665.

²³L. Lewi, "Recombinant DNA as a Political Pawn," *Nature Science*, vol. 79, Sept. 7, 1978, pp. 672-674.

the question of risk, RAC proposed revisions to the Guidelines, which placed most experiments at a lower containment level. They were published for public comment in September 1977. * As with the original Guidelines, public hearings were held in the course of a 2-day meeting of the Advisory Committee to the Director in December 1977, in which a diverse group of individuals and organizations were permitted to comment. However, at this point, HEW took a much more active role in a situation that had been handled almost entirely by NIH.²⁴

When RAC's charter was renewed on June 30, 1978, Secretary Califano reserved the power to appoint its members instead of delegating it to the Director of NIH as in the past.** And the new proposed Guidelines, published in the Federal Register on July 28, 1978, were accompanied by an introductory statement by Secretary Califano announcing a 60 day public comment period to be followed by a public hearing before a departmental panel chaired by HEW General Counsel Peter Libassi. * * * The Secretary was particularly interested in comments on: new mechanisms to provide for future discretionary revision of the Guidelines; and the composition of the various advisory bodies, especially the RAC and the local Institutional Biosafety Committees (IBCs).²⁵

The public hearing called for by Secretary Califano and held on September 15, 1978, was a significant event in the history of Federal actions on the rDNA issue. Testimony was heard from representatives of industry, labor, the research community, and public interest groups; more than 170 letters of comment were received and subsequently reviewed. As a result, the revised final Guidelines of December 22, 1978, were significantly rewritten to increase public participation in the decisionmaking process:²⁶

- Twenty percent of the members of the IBCs had to represent the general public and could have no connection with the institution.
- Most of the records of the IBCs had to be publicly available.

● Shortly thereafter, in October 1977, the Final Environmental Impact Statement for the 1976 Guidelines was published.

D. Fredrickson, "A History of the Recombinant DNA Guidelines in the United States," *recombinant DNA Technical Bulletin*, vol. 2, July 1979, pp. 87, 90.

● The statement providing for delegation of authority that accompanied the updated Charter was not signed by Califano. See also, footnote 24.

* ● The other members of the HEW panel were Dr. Fredrickson, Julius Richmond, who was the Assistant Secretary for Health, and Henry Aaron, who was the Assistant Secretary for Planning and Evaluation.

43 F.R. : 33042, July 28, 1978.

Statement of Secretary Califano accompanying the revised Guidelines, 43 F.R. : 60080, Dec. 22, 1978.

- Major actions, such as decisions to except otherwise prohibited experiments on a case-by-case basis or to change the Guidelines, could be made only on the advice of RAC and after public and Federal agency comment.

The increased public responsiveness of the IBC's was crucial, since the revised Guidelines placed major responsibility for compliance on them. This had been proposed in the July version and had not been changed by the hearings. * Califano also announced he would appoint 14 new members to the RAC, including people knowledgeable in fields such as law, public policy, ethics, the environment, and public health. Z* ● All of these changes were envisioned to "provide the opportunity for those concerned to raise any ethical issues posed by recombinant DNA research" and to change the role of the RAC to "serve as the principal advisory body to the Director of NIH and the Secretary of HEW on recombinant DNA Policy."²⁸ * * *

In addition to broadening public participation, Califano attempted to deal with a major limitation of the Federal response—the Guidelines did not cover private research. He directed the Food and Drug Administration (FDA) to take steps to require that any firm seeking approval of a product requiring the use of rDNA techniques in its development or manufacture, demonstrate compliance with the Guidelines for the work done on that product; an FDA notice of its intention to propose such regulations accompanied the revised Guidelines in the Federal Register. In addition, he requested the Environmental Protection Agency (EPA) to review its regulatory authority in that area. He believed if both agencies could regulate research on products within their jurisdiction, "virtually all recombinant DNA research in this country would be brought under the requirements of the revised guidelines."²⁹ * In the meantime, the

● As part of the revision process, HEW held a meeting in October 1978 for RAC chairpersons in order to exchange information and experiences gained under the 1976 Guidelines.

²⁴Ibid.

● ● This was implemented by an amendment to the RAC Charter on Dec. 28, 1978, which increased the membership to 25 and changed the composition to the following categories: 1) at least eight specialists in molecular biology or rDNA research; 2) at least six specialists in other scientific fields; and 3) at least six persons knowledgeable in law, public policy, the environment, and public or occupational health. In addition, the Charter was amended to grant nonvoting representation to representatives of various Federal agencies.

²⁵Ibid.

● * ● The Charter was never amended to change or delete the final sentence of the "Purpose" section, which states, "This committee is a technical committee, established to look at a specific problem."

²⁶"Ibid., p. 60081.

revised Guidelines provided, for the first time, for voluntary registration of projects with NIH, in which the registrant would agree to abide only by the containment standards of the Guidelines.³¹

Other major changes were embodied in the new Guidelines. Because of the consensus that the experiments posed lower risks than originally thought, some types of experiments were exempted, while containment levels were lowered for almost all others. In order to provide greater flexibility, these Guidelines permitted exceptions on a case-by-case basis, and included procedures for their change on a piecemeal basis without going through the whole internal process at HEW. For major changes, the procedure was: 1) publication of the proposed changes in the Federal Register at least 30 days prior to a RAC meeting; 2) RAC consideration of the proposed changes; and 3) publication in the Federal Register of the final decision of the Director, NIH. The standard for all actions of the Director under the Guidelines was "no significant risk to health or to the environment."³² Lastly, the new Guidelines delegated project approval to the IBCs.

The problems posed by voluntary compliance and commercialization have continued to be addressed by NIH. In a second major revision to the Guidelines on January 29, 1980, a section (Part VI) was added to specify procedures for voluntary compliance. * • On

(continued from p. 318)

• Subsequently, California sent similar letters to the Secretaries of Agriculture (February 1979) and Labor (July 1979) requesting them to consider how their agencies' authorities could be used to require private sector rDNA research to comply with the Guidelines.

³⁰Minutes of the Interagency Committee on Recombinant DNA Research, p. 3, July 17, 1979, preprinted in *Recombinant DNA Research*, vol. 5, p. 132, et. seq.

³¹Sec. IV-F.3 1978 Guidelines.

³²Sec. IV-E-1-b.

• "Several responses to the FDA notice had questioned the agency's legal authority to regulate private rDNA research. Consequently, Dr. Fredrickson and Dr. Donald Kennedy, then Commissioner of Food and Drugs, developed a draft supplement to the Guidelines, specifying procedures for voluntary compliance by industry. It was published for comment on Aug. 3, 1979 (44 F.F. 45868) and incorporated as part of the proposed revised Guidelines of November 30, 1979. (44 F.F. 69210, 69247).

April 11, 1980, NIH published Physical Containment Recommendations for Large Scale Uses of Organisms Containing Recombinant DNA Molecules in the form of Draft Part VII to the Guidelines.³³ Besides setting large scale containment levels, this document recommends that the institution: appoint a biological safety officer with specified duties; and establish a worker health surveillance program for work requiring a high (P) containment level. Finally, a more ad hoc requirement has been used since October 1979 for approvals of industrial requests for cultures up to 750 liters (1); the approvals were conditioned on NIH designated observers being permitted by the companies to inspect their facilities.³⁴ At least one inspection has taken place.

On November 21, 1980, NIH adopted the third major revision to the Guidelines.³⁵ It contained these significant changes: institutions sponsoring the research are no longer required to register their projects with NIH pursuant to an informational document called a Memorandum of Understanding (MUA) whenever the containment levels are specified in the Guidelines; and NIH will no longer review IBC decisions on experiments for which containment levels are specified in the Guidelines.

On November 21, 1980, NIH also promulgated revised application procedures for large-scale proposals. The application must include the following information: 1) the registration document submitted to the local IBC; 2) the reason for wanting to exceed the 10-1 limit; 3) evidence that the rDNA to be used was rigorously characterized and free of harmful sequences; and 4) specification of the large-scale containment level proposed to be used as defined in the NIH Physical Containment Recommendations of April 11, 1980.

In addition to adding part VI to the Guidelines, the most significant change in the January 1980 Guidelines was the addition of sec. 111-0, which permitted most experiments using *E. coli* K-12 host-vector systems to be done at the lowest containment levels.

³³44 F.F. 24968 Apr. 11, 1980.

³⁴44 F.F. 69251, Nov. 30, 1979.

³⁵45 F.F. 77372, Nov. 21, 1980.