Asilomar Conference on Laboratory Precautions When Conducting Recombinant DNA Research – Case Summary

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Safe laboratory practices are an important element in the responsible conduct of research. They protect scientists, research assistants, laboratory technicians, and others from hazards that can arise during experimentation. The particular hazards that might arise vary according to the type of experimentation: the explosions or toxic gases that could result from chemical experiments are prevented or contained by different kinds of measures then are used to limit the health hazards posed by working with radioactive isotopes. In most areas, scientists are allowed – and even encouraged – to decide for themselves what experiments to undertake and how to construct and run their labs. In 1970, there were three main exceptions, and they applied more to questions of how to carry out research than to selecting topics for research: use of radioactive materials, use of tumor-causing viruses, and use of human subjects. In these areas, levels of risk to persons inside and outside the lab were perceived as great enough to justify having the government, either through the regular bureaucracy or through scientific agencies, set and enforce mandatory safety standards.

When genetics was poised at the threshold of recombinant DNA research and genetic manipulation techniques in the 1960s, the hazards such work might pose to lab personnel or to others were unknown. Many scientists and others believed they were likely to be significant. The primary concern in public discussion was whether hybrid organisms bred from recombinant DNA would cause new diseases or create varieties of plants or animals that would overwhelm and irretrievably change the natural environment. However, these fears linked up with more traditional concerns about laboratory safety since it was clear that 1) people working in labs would be exposed to hazards first and 2) the hazards of recombinant DNA research could be reduced if the experiments were kept small and the hybrids confined within the lab where they were created until their characteristics were better understood.

The discussions of laboratory safety took on a distinct character because of the frequency with which scientists considered trying to replicate natural gene sequences or to assemble human-made gene sequences by growing them in bacteria of the species Escherichia coli. E. coli, as it is generally called, is very widespread. It had become a favorite component of genetic research in the 1950s because it was

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easy to grow, tolerant of a wide range of temperatures, and reproduced rapidly. Rapid reproduction allowed researchers to follow genes and gene mutations—both natural and human-induced—clearly. In the 1960s and early 1970s most scientific laboratories were using a particular strain of E. coli known as K12, which was generally believed to have been evolved in a way that it could no longer live outside lab tissue cultures. Yet when some experimenters proposed taking genetic material from viruses and seeing if E. coli K12 would pick it up, microbiologists expressed alarm because they feared that genetically enhanced K12 might come into contact with the other strain of E. coli that inhabits a small portion of human intestines and create a human health hazard.

Many of the scientists doing early rDNA research were slow to make this connection, however, because of their training. As Norman Zinder, then a senior microbiologist at Rockefeller University, recalled in 1975, most of the early participants in rDNA research "were trained in biochemistry or molecular biology and had very little microbiological training, and therefore were not familiar with the procedures you'd generally use to keep the investigator himself from getting infected, no less the general population."[1] When scientists trained in microbiology and accustomed to following regulations about lab design, lab conditions, and protection of lab personnel heard about proposed experiments involving viruses and bacteria they called their colleagues' attention to the biohazards.

In most fields of science, such discussions would have resulted in peer pressure to be careful but not in suggestions to halt experiments altogether. Yet in 1974 leading experimenters agreed to suspend their work with recombinant DNA (rDNA) until the hazards could be assessed and guidelines for the conduct of research developed. Assessing the hazards and recommending guidelines became the tasks of the February 1975 Asilomar International Conference on Recombinant DNA Molecule Research. Since the Asilomar Conference has been proposed as a model for considering whether and how to undertake research in emerging areas of science and technology, the conference and its place in the development of government regulations governing rDNA research deserves study.[2]

Background

James Watson's and Francis Crick's suggestion that DNA molecules have a double helix structure in 1953 resolved many questions in theoretical genetics. Work confirming their suggestion also indicated that it would be possible to manipulate genetic material directly by altering DNA molecules, opening up a new and potentially more precise method of developing new varieties of life forms ranging from microorganisms to plants and animals. Instead of relying on crossbreeding whole organisms, better understanding of DNA molecules would allow researchers and breeders to identify the particular gene or gene sequence that instruct a developing organism to express particular traits, un-strand DNA molecules taken from that organism, remove the desired gene or gene sequence, un-strand DNA molecules from some other organism, insert the clipped sequence, re-strand those DNA molecules, insert the resulting recombinant DNA molecules into cell tissue serving as a growing medium, multiply the cells containing the rDNA with cell culture techniques, and insert that recombinant DNA into an individual of the organism to be hybridized.

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[1] Interview by Charles Weiner, 2 September 1975, quoted in Sheldon Krimsky. 1982. Genetic Alchemy: The Social History of the recombinant DNA Controversy (Cambridge, MA: MIT Press), p. 25.

[2] E.g., Alexis Madrigal, "Climate Hackers want to write their own rules" Wired Science site March 23 2010. Accessed June 21, 2010. http://www.wired.com/wiredscience/2010/03/geoengineering-asilomar/#izxx)rWRyfl36.

While notions of "gene splicing" or "genetic engineering" by creating recombinant DNA were abstract dreams in the 1950s, they were approaching reality in the early 1970s. Many scientists and others were excited by the possibilities of having more precise breeding tools; in their view, greater genetic knowledge and application of gene splicing techniques would allow better treatment of disease, reversal of genetically-based congenital disorders, and faster development of new plant varieties with a wider range of desirable characteristics. Others feared that potential for catastrophic consequences and believed that gene splicing should not be undertaken unless and until scientists were certain they could prevent catastrophe. They believed that the probability of unintentionally creating dangerous organisms—virulent "super" versions of disease-causing viruses or bacteria, strange and invasive life forms that push others out of habitats—because the ways genes and gene sequences interact were not well understood was too high to be ignored. They also feared intentional misuse of the techniques to create new biological weapons. The possibility of intentional misuse was prominent in many minds during the 1950s and 1960s as the Cold War continued; the longstanding international bans on using asphyxiating gasses would not apply to infectious organisms, and the even older ban on using poisoned weapons might not hold if warring nations believed using biological weapons to spread infections among enemy troops or populations would give them an advantage in warfare. However, they were abating by the early 1970s because the Soviet Union and the USA were making progress on agreements specifically banning development and use of biological weapons.

The tenor of debate about rDNA research was also influenced by the context of the time. The practical implications of rDNA techniques began to be perceived in the late 1960s, a time of heated debate in the USA and other Western societies about the role of science in society. Some portions of this debate were aspects of the wider contention over the fundamental structure of society raging at the time, but others were focused on the more immediate implications of scientific research on society. Growing opposition to US involvement in Vietnam in the 1960s had shattered the Cold War consensus on foreign policy and opened up opportunities for reviving and spreading Marxist critiques of capitalist society. National organizations of politically radical scientists or health care professionals like Science for the People,[3] the Medical Committee for Human Rights, or and more local groups like the Science Action Coordinating Committee at MIT regarded science as functioning to prop up the capitalist system, and sought to realign it to the service of socialist revolution. A larger fraction of scientists took reformist political stances and tended to feel that scientists should be more active in using their expertise to inform and instruct the public about scientific developments and their social implications. Many of the reformists were members of national organizations like the Federation of American Scientists, the Society for Social Responsibility in Science, and the Scientists' Institute for Public Information.

As the prospects of genetic modification came closer, both the radicals and the moderates agreed that its implications needed to be discussed openly in forums available to the general public. However, they diverged on questions of how decisions about the conduct of rDNA experiments should be regulated. The radicals preferred much more involvement by the general public in decisions about what lines of research should be pursued and how allowable research should be conducted. The reformists agreed that it was time to pay more attention to the broader social and environmental implications of particular lines of research, but believed that scientists themselves should take the lead in suggesting policies because they

[3] Organized in 1969 as Scientists and Engineers for Social and Political Action and using the motto "Science for the People;" the simpler and more vivid motto soon became the group's name.

had the expertise needed to determine whether the likely risks of some line of research outweighed the likely benefits.

The debates about the consequences of rDNA research also occurred just as bioethics – inquiry into the moral and ethical foundations of scientific work in the medical, life, and biological sciences – began to emerge as a distinct field. Bioethics discussions addressed whether particular types of scientific work should be done, how that work should be done (particularly if it put people at risk of disease or death), and how far society should leave decisions about the direction and conduct of scientific research to the scientists themselves. The Hastings Center,[4] organized in 1969, was publishing a bimonthly journal (the Hastings Center Report), holding interdisciplinary workshops on ethical questions, and producing teaching materials by the time the rDNA debates began. The Kennedy Institute of Ethics at Georgetown University began similar work around 1970. By 1974, the ethics committee of the Biophysical Society was also discussing the implications of rDNA research.

Rising Concern about Safe Laboratory Practices

It was in this context of increasing discussion of the social and political implications of new scientific knowledge and growing concern with ethics that scientists coming to rDNA work from other fields were learning about the safety concerns raised by rDNA research generally and particularly with experiments using viruses and bacteria. Though deriving from somewhat different sources, three streams of concern came together in 1972-73 to inspire wide-ranging discussions among the scientists working on rDNA or related questions producing broad consensus on two points – that too little was known about the actual nature and extent of risk posed by rDNA experiments and that public confidence in the safety of rDNA research would be maintained only by accepting some explicit government regulation regarding laboratory design and work routines.

The origins of the first stream of concern go back to the 1960s when several geneticists and microbiologists began using phages, viruses that infect bacteria, to learn about gene expression and protein synthesis in prokaryotes (bacteria and blue-green algae). Scientists first noticed that phages often picked up pieces of the genetic composition of the bacterium they had already infected and carried it to the next bacterium they succeeded in infecting. Then they were able to isolate and study the effects of this transferred genetic material. Since phages infect bacteria rather than plants, animals, or humans, the research was considered completely safe and usually conducted in open laboratories without taking precautions against biohazards. By the late 1960s some scientists were suggesting that animal tumor viruses might be able to provide the same sort of probe for genetic effects in animal cells that phages did in bacteria cells. By 1970, Paul Berg of Stanford University, already a leading genetic researcher, was interested in following up these suggestions.

Though the role of viruses in causing human cancer was unclear, several viruses were known to cause tumors in animals by direct exposure or by transforming the properties of normal cells in cell cultures to make them sufficiently malignant to cause tumors in an animal injected with the cultured cells. Berg and his group planned to use SV40, a monkey virus known to virologists as being very good at transforming human cells growing in tissue culture into malignant cells, as the carrier of genetic material. While trying to

[4] Formally named the Institute of Society, Ethics, and the Life Sciences, but generally known after its location in Hastings-on-the-Hudson, New York.

develop a way to insert other genes into an SV40 chromosome, which proved harder than expected, Berg suggested to Janet Mertz, one of his graduate students, that she determine whether SV40 genes injected into bacteria would be taken up in the bacteria's own DNA and lead the bacteria to express SV40 traits. They decided to use E. coli K12 because bacteria of that strain, unlike most E. coli, can exchange genetic material with each other. As word of Berg's plans circulated among microbiologists with greater awareness of biohazards in general and those arising from use of E. coli in particular in mid-1971, they urged him to call off the experiments. This he did in early 1972 after further discussions with other scientists.

A few months later, a second stream of concern about biohazards arose after Andrew Lewis, Jr., a scientist at the National Institute of Allergy and Infectious Diseases (NIAID), started receiving requests for samples of hybrid material he had developed combining elements of SV40 virus and a form of human adenovirus. Normal scientific courtesy indicated that a scientist should provide samples of a hybrid after publishing the results of research on it. However, Lewis believed the hybrids posed significant biohazards, and wanted to provide samples only to scientists who were aware of the risks involved and had lab facilities with ventilation and containment systems adequate for safe handling of viruses. In November 1972, he asked the Director of NIAID for guidance about how he should respond to requests for samples. The Director and more senior scientists at NIAID agreed that he should limit distribution and also began discussions with the NIH and the Center for Disease Control (which establishes the safety regulations for transportation of infectious material) about how to control its distribution and use. These discussions had just begun when the possible biohazards of rDNA research became a hotter topic among scientists.

The third stream of concern stemmed from research on plasmids at the Stanford Medical School. It was common scientific knowledge that plasmids, small bits of DNA that float around within bacteria, could carry genetic material. Stanley Cohen, then a relatively young scientist, showed that plasmids could be used for inserting foreign genetic material into E. coli. By mid 1973 John Morrow, a more senior scientist at Stanford Medical School, Herbert Boyer, a senior scientist at the University of California San Francisco, and Cohen had used plasmids to replicate DNA from the frog species Xenopus in E.coli. A different and unexpected addition to the methods of mixing DNA from different organisms arose almost simultaneously. Herbert Boyer had earlier developed a restriction enzyme from E. coli, which he called EcoR1, using it in his own research and also supplying some to Paul Berg's research group at Stanford. Two of Berg's junior collaborators, graduate student Julie Mertz and Assistant Professor Ronald Davis, followed up on anomalous observations in their experiments and found that SV40 DNA was able to reconstitute itself on its own after being split into pieces by EcoR1. This was not expected; both basic biology (restriction enzymes are a bacteria's natural defense against outside DNA) and all experience with them indicated that restriction enzymes would cut DNA in such a way that it could not spontaneously reassemble. However EcoR1 produced cuts in a different pattern leaving what scientists called "sticky ends" that could be rejoined – either to constitute the whole DNA of which they were part of or to assemble fragments of DNA from more than one organism into a coherent molecule. This ability to reassemble spontaneously made "gene splicing" much less difficult.

As this work proceeded in 1973, two sets of discussions about the biohazards would arise in scientific work. The first, the Conference on Biohazards in Biological Research, was held in January at the Asilomar Conference Center in Pacific Grove California. It was inspired primarily by Paul Berg with Robert Pollock of Cold Spring Harbor Laboratory, Michael Oxman of the Harvard Medical School, and Al Hellman of the National Cancer Institute doing most of the organizational work. Financial support came from the National Science Foundation and the National Cancer Institute, which were interested in the topic because of the increase in cancer research after adoption of the National Cancer Act in 1971. This conference, sometimes

known as Asilomar I, involved approximately 100 scientists from around the United States and featured papers on the potential risks of using viruses in a range of biological research; rDNA experiments were addressed only incidentally. Participants discussed what was known about the risks of rDNA work, concluded that little was known, and ended with agreement that scientists should get more information before they undertook large scale rDNA work.[5]

By this time scientific discussion was focusing on eleven potential hazards. Seven raised concerns about all rDNA experiments that shaded into the terms of the broader public debate about whether recombinant DNA would be safe and whether "genetic engineering" would be beneficial or harmful to society as a whole:

1. Any gene can be harmful. Most risk arguments in the 1970s looked at the character of individual genes or particular gene sequences in the donor organism (the organism from which the DNA is extracted), the cells in which it is grown, or the host organism (the organism in which the DNA is inserted). Scientists raising this argument maintained that the way a transplanted gene functions depend not only on its own characteristics but also on where it is located in the rDNA molecule in relation to other genes, and on the entire cellular environment within which the genetic material exists. This was an attack on the common belief among biologists that each gene has a particular product, and was heavily inspired by notions of the emergent properties being developed among advocates of complexity theory.

2. Shotgun cloning. This term covered experiments in which the whole genome of an organism was exposed to restriction enzymes, an unpredictable number of DNA fragments were produced, one or more fragments inserted into cells in a cell growth medium, and those cells inserted into some host organism. Researchers would then be able to examine the random fragments for special functional characteristics. Since these experiments were being proposed before either the donor organism's genome or the host organism's genome had been completely characterized, critics of shotgun cloning feared that such work would produce new genetic sequences harming the host organism.

3. Crossing species barriers. Scientists were well aware that interspecies breeding is limited in nature. One matter for debate was whether those natural limits functioned as a biological regulator limiting the amount and or the speed of gene mutation. The other, more immediately of concern in laboratory work, was whether prokaryotes (bacteria) and eukaryotes (protozoa, fungi, plants, animals and humans) exchanged genes in nature. If they did, experiments recombining their DNA would not be very far from what happens in nature and would be perceived as having lower risks than if they did not.

4. Autoimmune effects. This debate came up as prospects for developing rDNA versions of human insulin or growth hormones came into view. Concern focused on the possibility that DNA coding for some animal protein cloned in E. coli might migrate to animals or humans and trigger immune system responses in which both the rDNA intruder and natural E. coli would be attacked, leaving the animal or human in a seriously weakened state causing chronic illness or death.

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[5] A. Hellman, M.N. Oxman, and R. Pollack, eds. 1973. "Biohazards in Biological Research." Proceedings of a Conference held at the Asilomar Conference Center, Pacific Grove, California, 22-24 January 1973. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1973

5. Creating or enhancing plant pathogens. Most discussion of recombinant DNA hazards focused on hazards to humans, but scientists interested in plants worried that rDNA or enhanced plant pathogens might transfer to and threaten the survival of one or more species of plant.

6. Making new types of hybrid plasmids. Though there is considerable plasmid exchange between closely related species in nature, many scientists feared that engineering new plasmids in the course of work with viruses or animal tumors would either create new pathogens, or increase the virulence or range of existing pathogens.

7. Spreading resistance to antibiotics. Some researchers proposed using R factors (antibiotic resistance factors) to move targeted genes so that fragments of genetic material could be tracked to determine whether combinations are taking. This overlapped with other concerns because of proposed experiments that would put R factors into plasmids that would be combined into E. coli bacteria. Some scientists feared that R factor-enhanced E. coli might spread to humans or animals and decrease the effectiveness of antibiotic treatments.

Another four concerns focused mainly on the particulars of certain proposed experiments:

1. Making recombinant viruses. Some experimenters proposed experiments that would combine a known human pathogen with an animal cancer virus; these triggered fears that the resulting hybrid would at the least have the combined pathogenic characteristics of the tumor and the human virus or might prove even more potent.

2. Producing E. coli with troublesome proteins by inserting “foreign” genes or gene sequences into its DNA. DNA is nature’s set of instructions to organisms about how to assemble their proteins, and the concern here was that proteins resulting from the inserted DNA could disrupt normal human metabolic functions or break an immunological threshold.

3. Creating E. coli pathogens. Researchers were sufficiently attentive to the risks of using E. coli in experiments because it is symbiotic with humans and animals to prefer using a specially synthesized version, E. coli K12, believed to be unable to survive outside laboratories. However, some scientists believed that even E. coli K12 could take on novel properties making it a pathogen or competitive with the tougher E. coli strains able to survive in natural environments.

4. Transferring pathogenic or otherwise harmful DNA from E. coli K12 to wild strains of E. coli. Even scientists who agreed that E. coli K12 could not survive outside a lab or colonize human guts still worried that genetic information might be exchanged between E. coli K12 and other strains of E. coli through plasmid transfer before the E. coli K12 dies and then go on to create biohazards.

The second, and more immediately influential set of scientists’ discussions regarding potential hazards occurred at the June 1973 Gordon Conference on Nucleic Acids. Gordon Conferences are five-day gatherings of scientists, with the topic and hence the participants varying from session to session. Some leading scientists serve as the organizers and select other participants based on the abstracts of research

they submit. Conference ground rules specify that participants may not use any information presented during presentations or informal discussions at a Gordon Conference without the permission of the person who provided it. Presentations may not be recorded, nor are the proceedings published. This makes Gordon Conferences a venue where scientists can network and let each other know what they are working on. The June 1973 session was organized by Peter Söll of Yale University and Maxine Singer of the NIAID. 143 scientists signed up to participate, 114 from the USA, seven from England, six from Germany, five from Canada, five from Japan, and one each from Australia, France, India, Scotland, Sweden, and Switzerland. Most of the participants were affiliated with universities, but eight came from private industry, 10 from nonprofit private institutions and 17 from government-sponsored laboratories. [6]

During a session on "Bacterial enzymes in the analysis of DNA" held on Thursday morning, the fourth day of the conference, participants mentioned successful isolation of several new DNA restriction enzymes. After Herbert Boyer reported on his work with the restriction enzyme EcoR1 and suggested how it might be used to construct new plasmids, another participant said, "Well, now we can put together any DNAs we want to."[7] This remark attracted much attention and participants wanted to discuss both the hazards and the social implications of recombinant DNA work. Singer and Söll responded by setting aside a half-hour the following morning for such discussion. Those who attended this short session agreed that a joint letter should be written to the National Academy of Sciences and the National Academy of Medicine asking them to establish an expert panel to study the biohazards of rDNA research and that this letter should be signed by every participant who wants to sign. A slim majority also agreed the letter should be publicized within the scientific community. Because the Friday session was held after many of the conference participants had already left town, Singer and Söll decided to send a draft of the letter to all the conference participants so they would have an opportunity to express their views on whether to send the letter and whether to publicize it, join the list of signatories, and suggest revisions to the letter itself. Among the wider set of all participants there was strong support for sending a letter to the National Academies, some discussion of exactly how to word it, and a slim majority in favor of getting it published in Science.[8]

The Moratorium and the Asilomar Conference

The National Academy responded by encouraging formation of an informal study group to consider the letter and formulate a response. Paul Berg was asked to head it and recruit its other members. David Baltimore, Herman Lewis, Daniel Nathans, Richard Roblin III, Sherman Weissman, and Norton Zinder were recruited and, after some preliminary correspondence, gathered in April 1974 at MIT to "consider whether or not there is a serious problem growing out of present and projected experiments involving construction of hybrid DNA molecules" and what to do if they concluded there was a serious problem. Baltimore and Roblin were ready to urge a moratorium on a wide range of rDNA experiments; some of the others felt that suggesting a moratorium infringed on scientists' rights to design their own inquiries. By the end of their one-day meeting, the eight agreed to recommend:

a) all scientists avoid undertaking the most dangerous types of rDNA experiments until risks are better understood and guidelines can be developed,

[6] Krimsky 1982 pages 71 and 72. Krimsky notes that 130 of the 143 scientists registered for the conference actually attended.

[7] Maxine Singer's recollection of the discussions quoted in Michael Rogers. 1977. Biohazard (New York: Alfred A. Knopf), p. 42.

[8] Maxine Singer and Dieter Söll. 1973. "Letter: Guidelines for DNA hybrid molecules," Science, 181: 1114 (21 Sept. 1973).

b) the US National Institutes of Health (NIH) establish an advisory committee to oversee experiments designed to assess the likelihood of undesirable results and hence put risk assessment on a firmer empirical basis, develop procedures for preventing the spread of rDNA, and develop guidelines for safe practice in rDNA research, and

c) the NIH convene an international conference of scientists to assess the hazards and propose guidelines.[9]

They divided rDNA experiments into three groups: 1) experiments in which genes triggering formation of antibiotic resistance factors or of toxins are linked to plasmids and then replicated in a bacteria cell culture, 2) experiments with animal viruses, and 3) experiments randomly linking elements of animal DNA to bacterial plasmids and then inserting the plasmid into a bacteria cell culture. All eight participants agreed the first two types were sufficiently dangerous to be avoided until guidelines had been developed; the third type inspired disagreement because it covered a much wider set of experiments with varying degrees of perceived hazard.

They also hesitated to recommend a blanket moratorium because at that time there was no precedent for imposing moratoria on specific types of experiments in a newly emerging field. The closest analog was an agreement among physicists outside Germany, Japan, and Italy in April 1940 to avoid publication of results of experiments in nuclear physics lest they help the Axis develop atomic bombs.[10] Thus even the participants most committed to recommending a moratorium were unsure how other scientists would react. They did agree they needed to communicate their concerns to the wider scientific community, since the apparent power and usefulness of rDNA would attract lots of new researchers to the field. They decided to publicize their concerns through letters to the editors of Science, the leading scientific weekly in the USA, and Nature, its counterpart in the UK.

Others' reactions were generally supportive. Four other leading researchers, Herbert Boyer, Stanley Cohen, Ronald Davis and David Hogness, became co-signers. A transmission error dropping some words in an early sentence in the version published in Nature left the impression that the signers were proposing that scientists also halt work on naturally-occurring drug resistant plasmids and inspired some sharp reactions from British plasmid researchers. However, other leading British scientists, including Michael Stoker, head of the Imperial Cancer Research Fund and Kenneth Murray of the University of Edinburgh, supported the call for a moratorium.[11]

Public interest in the US was raised by headlines like "Scientists urge ban on Genetic Research." Word of the moratorium also reached further; a commercial supplier of restriction enzymes shipping a supply to Maxine Singer's lab later in the summer also included a printed notice saying the enzymes had been supplied on the understanding that they would not be used for the kinds of experiments the Berg letter said

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[9] As given in the final version of their recommendations, which were published in Science in July. See Paul Berg et al. 1974. "Potential biohazards of recombinant DNA molecules," Science 185:303 (26 July 1974), Nature 250:175 (July 1974), and Proceedings of the National Academy of Sciences 71: 2593-2594 (July 1974).

[10] Rogers 1977, p. 103.

[11] K. Murray. 1974. "Alternative experiments?" Nature 250: 279; M. Stoker. 1974. "Molecular dirty tricks ban." Nature 250:278.

should be avoided.[12] Public support for the moratorium was even stronger in the UK, where there had been a major biohazard scare in March 1973. Smallpox virus from a lab at the London School of Hygiene and Tropical Medicine infected a visiting technician, who transmitted it to others outside the lab. Because smallpox vaccination was widespread in the UK and health authorities worked to trace and isolate the technician's contacts, only two people died from the virus. The incident left the public worried and as discussions of biohazards in rDNA research intensified, the British Medical Research Council essentially banned all the experiments mentioned in the Berg letter and convened a working party chaired by Lord Ashby to assess the benefits and hazards of recombinant DNA work.

The National Academy of Sciences and the NIH responded favorably to the proposals. The Academy designated the Berg group as the Assembly of Life Sciences Committee on Recombinant DNA Molecules and endorsed its recommendations. It also agreed to support holding the larger conference, including scientists from outside the USA, to assess the hazards more fully. Committee Chair Paul Berg was asked to lead the conference organizing committee and selected the other members with approval of the National Academy. He asked fellow committee members David Baltimore and Richard Roblin, Maxine Singer, because of her role in organizing discussions at the Gordon Conference, Sydney Brenner, a senior scientist at the UK Medical Research Council's Laboratory for Molecular Biology, and Niels Jerne of the Basel Institute for Immunology in Switzerland, who was also chairman of the European Molecular Biology Organization's council. (Jerne ultimately did not participate, so is not listed as a member in the Asilomar Conference report).

The organizing committee met in mid-September and chose chairs for the three working groups that would be asked to develop papers addressing whether and how particular types of rDNA research should be conducted: 1) use of plasmids, 2) rDNA created with eukaryote DNA, and 3) rDNA created with viruses. Richard Novick, a microbiologist at the Public Health Research Center in New York City and an expert on plasmid transmission of DNA material was asked to chair the plasmid working group. Donald Brown of the Carnegie Institution and an expert on gene expression and control was asked to chair the eukaryote working group. Berg knew that Brown was interested in experimenting with eukaryote to prokaryote DNA transfers but also prepared to accept that some experiments might be too risky to undertake. Aaron J. Shatkin of the Roche Institute of Molecular Biology in Nutley, New Jersey, was asked to chair the virus working group. Employed in a company-supported laboratory, Shatkin was knowledgeable about tumor viruses but not working on them at the time; the organizers thus felt he would be perceived as knowledgeable about the science but open-minded about whether any rDNA experiments with viruses should be allowed. The chairs then recruited other members of their working group. Novick, a member of the American Society for Microbiology's task force on plasmid nomenclature, asked the other members of that task force to participate in the plasmid working group. The others drew on their networks of acquaintances.[13]

The other participants in the conference were selected in similar fashion. Berg asked the organizing committee and working group chairs for recommendations. He then made a list of about 150 scientists and circulated it among the same people for comment. Members of the group brought different concerns to this exercise. Novick wanted to have senior scientists who had also expressed concerns about the wider social consequences of creating rDNA working in the basic areas of rDNA research. The organizers also felt

[12] Singer recollection quoted in Rogers 1977, p. 48.
[13] Appendix C lists the members.

since industrial applications of rDNA technology would create the most hazards because they would involve larger scale production of genetic material in larger quantities of tissue culture, they should include industry-employed scientists. Thus senior researchers in the research divisions or corporate-funded laboratories of General Electric, Merck, Roche, and Searle attended. At least some of the organizers wanted to include scientists who had been outspoken in addressing the broader social implications, and invited Jonathan Beckwith, a microbiologist at the Harvard Medical School and a member of Science for the People. He was unable to attend, and the organizers decided against inviting a postdoctoral researcher who was also a member of Science for the People that Beckwith suggested instead because they wanted senior participants rather than representatives of particular organizations. Jonathan King of MIT, who specialized in the genetics of bacteria phages and had also taken positions on social issues, was considered but also did not attend.[14] This would strengthen criticism from those who believed the Asilomar Conference should address the "whether" question as well as the "how" question.

The 153 participants who came to the Asilomar Conference Center in February 1975 included 83 molecular biologists from the USA, 50 molecular biologists from other countries, 16 journalists and 4 lawyers. Conference discussions were organized around reports from the 3 working groups, and a separate session was conducted on legal and ethical issues arising from rDNA experiments. Even with the focus on hazards of rDNA research rather than the broader social issues of whether it should be done at all and how to keep it from being misused for biological warfare,[15] the participants engaged in a very intense debate because the consensus that rDNA research involves real hazards was insufficient to induce quick agreement on the nature of the hazards or the types of laboratory work that would produce them. Some were reluctant to characterize any experiments as hazardous for fear of locking in the moratorium as a permanent ban. Others were concerned that unless the scientists showed they were taking possible hazards seriously, governments would be pressed to ban rDNA research because public opinion was very skeptical of it at this time. As Paul Berg, one of the Asilomar Conference conveners, recalled later, "What turned the debate around was the suggestion to assign a risk estimate to the different types of experiments envisaged, and to apply safety guidelines of varying stringency according to the degree of risk."[16] This enabled participants to disaggregate rDNA research into more and less hazardous types of experiments, and think in terms of a range of possibilities (including continuing the moratorium on certain experiments) rather than an all-or-nothing binary. Sydney Brenner added another crucial element: the notion of consciously developing plasmids, phages, and bacteria that could not survive outside lab tissue culture vessels.

The animal virus working group suggested work with recombinant DNA should proceed under the same laboratory guidelines as used by the National Cancer Institute for laboratory work with tumor-causing viruses. At the time NCI had three categories of risk: low, moderate, and high. The working group suggested experiments on recombinants containing animal virus genes be done under conditions satisfying NCI regulations for moderate risk experiments, experiments involving purified segments of virus DNA not associated with causing disease be done under NCI low risk containment standards, and experiments with highly pathogenic viruses be done under NCI high containment standards. While most of the working

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[14] Krimsky 1982, p. 111, who adds that Berg and Baltimore believed King had been invited but King said he had not been invited.

[15] As Baltimore reminded participants in his opening remarks. Quoted in Charles Weiner, "Drawing the Line in Genetic Engineering: Self-Regulation and Public Participation" Perspectives in Biology and Medicine 44.2 (2001) 211-212.

[16] Paul Berg. 2008. "Meetings that changed the world: Asilomar 1975: DNA modification secured," *Nature* 455 (18 Sept 2008) p. 290

group anticipated most experiments with viruses would come within the moderate risk category, one member, Andrew Lewis, took a more cautious position and added a minority report saying more data on the risks was needed before proceeding with any rDNA work.[17] The eukaryote working group, which knew about the plasmid working group's discussions, adopted the plasmid group classification scheme for experiments but also suggested some broad principles to guide risk assessment: 1) the risks of an experiment with a eukaryotic virus are not less than that of the virus itself -- thus any rDNA should be regarded as being at least as hazardous as its most hazardous component, 2) DNA from higher mammals have greater potential for human hazard than DNA from lower animals because viruses are more likely to move between species that are closely related to one another biologically. Using those guidelines eukaryote working group classified most recombinant DNA experiments within classes two through six of the plasmid working group's classification.

The plasmids and bacterial DNA working group adopted a three-step approach to risk assessment: 1) determining the biohazard potential of the experiment, 2) matching the level of biohazard potential with the strictness of containment measures to be adopted in the lab, and 3) banning experiments involving organisms that would be hazardous even if only a few of them escaped the lab. This led the working group to divide all rDNA experiments into 6 categories:

- Class I. Biohazards can be assessed and are known to be insignificant; genetic exchange occurs naturally.
- Class II. Biohazards can be reasonably assessed and one expects them to be minimal; genetic exchange occurs naturally.
- Class III. Experiments in which the biohazard usually cannot be totally predicted, but (1) the donor DNA will not significantly increase the pathogenicity of the recipient, nor significantly alter its ecological potential; (2) the pathogenicity of genetically altered microorganisms or its parents is minimal; (3) genetically altered microorganisms do not escape treatment of infections caused by it.
- Class IV. Experiments in which the biohazards are usually unknown and cannot be accurately assessed; transplanted DNA is judged potentially significant in affecting either the ecological potential or pathogenicity of the recipient of organism.
- Classic V. Experiments in which the biohazards are usually unknown; transplanted DNA could severely affect the pathogenicity or ecological potential of the recipient of organism.
- Class VI. Experiments in which the biohazards are judged to be of such great potential severity as to preclude performance of the experiment, under any circumstances at the present time.[18]

The working group also insisted that scientists contemplating work with rDNA needed to have adequate microbiological training. This was partly to address questions of handling material in the lab, but it was also

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[17] Report of the animal virus working group, Recombinant DNA controversy collection, Institute Archives and Special Collections, MIT Libraries Cambridge, Massachusetts, p. 19 quoted in Krimsky 1982, page 130.

[18] Plasmid Working Group. 1975. "Proposed guidelines on potential biohazards associated with experiments involving genetically altered microorganisms," Asilomar Conference, 24 February 1975. Recombinant DNA controversy collection, Institute Archives and Special Collections, MIT Libraries Cambridge, Massachusetts. p.19 quoted in Krimsky 1982, page 129.

intended to reframing the scientists' approach to perceiving risk. The working group was concerned that chemists coming into the field would think about risk only in terms of the direct and anticipated interactions among molecules considered as chemicals. It wanted everyone working with rDNA to be thinking in microbiological terms, not only about the specific genetic parts being manipulated but also the whole being of a genetically modified organism in the environment. As the working group report put it, "a micro organism is not simply a 'warm body' to house a recombinant DNA molecule of interest."[19]

The presentation on liability by Roger Dworkin of the University of Indiana Law School reinforced the momentum in favor of adopting required lab practices. He outlined how scientists could be held accountable under liability law for harm done to others either because of the way the work was done or because a hazardous experiment was undertaken in insufficient conditions of safety. He also indicated that because they are workplaces laboratory conditions could be regulated by the Department of Labor under the Occupational Safety and Health Act (OSHA).

Brenner's suggestion for "disarming" phages, plasmids, and bacteria to be used in rDNA experiments by breeding them to be nonviable outside of lab conditions led to some informal lunch-time discussions during the Asilomar Conference, and a number of workshops afterward. These suggested using ways of inducing nonviability and categories to classify the safety of disabled host organisms. The scheme of dividing organisms into EK1, EK2, and EK3 classes and the criteria qualifying organisms for each class was not outlined until the first set of NIH Guidelines were issued in 1976.

The conference's unprecedented character inspired considerable uncertainty about how it should proceed. The organizing committee had been commissioned by the National Academy of Sciences to produce a report to be provided to the National Institutes of Health. Thus it would have been possible for the members of the organizing committee to issue a summary of discussion and its own sense of what regulations participants endorsed. Other participants wanted to have votes, but as long as members of the organizing committee were unsure how the vote would go they were wary of committing to any voting process. Brenner forced the issue by calling for votes. On the key question of whether to recommend banning any experiments, the participants adopted a middle ground between the plasmid working group's suggestion for a ban on certain types and the other two working group's silence by adopting a recommendation that certain experiments should not be done even in the highest level containment facilities currently available. The lack of high containment facilities and the cost of constructing them made this statement a de facto ban, at least for the short to medium term.

Asilomar Conference participants ultimately agreed to these recommendations:

a) measures to assure that any organism created with rDNA is contained within the lab are an essential component of experimental design;

b) the extent of containment measures should match the anticipated risk of the experiment;

c) experimenters should create biological barriers to escape the spread of organisms bred with recombinant DNA by such measures as using bacterial hosts for DNA growth that cannot survive outside a lab;

[19]Plasmid Working Group 1975, p. 19 quoted in Krimsky 1982, page 130.

d) experimenters must strictly observe the best microbiological practices in lab work, and

e) different types of rDNA experiment pose different levels of risk; therefore it is appropriate to categorize experiments as minimal, low, moderate, and high risk activities and to develop distinct containment recommendations for each category of experiments;

f) certain experiments should not be done now -- experiments that pose severe biohazard risk in current conditions of knowledge and containment measures, in particular experimentation with known carcinogens, genes that produce toxics, and genes that determine antibiotic resistance, and large-scale experiments (using 10 or more liters of tissue culture) using rDNA capable of making hybrids potentially harmful to humans, animals, or plants.[20]

The conference summary statement divided rDNA experiments into four risk categories:

Minimal containment	DNA recombinant from prokaryotes known to exchange genetic information naturally
Low containment	Creation and propagation of recombinant DNA molecules derived from species that ordinarily do not exchange genetic information ("novel biotypes")
Moderate containment	DNA recombinants involving pathogenic organisms capable of increasing pathogenicity of recipient species or that trigger new metabolic activities not native to the species used, or that can extend the range of resistance of established human pathogens to antibiotics or disinfectants; Rigorously purified and characterized segments of non-cancer viral genomes; non-transferring regions of cancer virus DNAs; DNA from nonviral agents in animal cells; DNA from primate genomes; uncharacterized DNA of warm-blooded vertebrates.
High containment	Some experiments with highly pathogenic organisms; Experiments with potential to extend the host range of many virulent organisms.

[20] Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin III, and Maxine F. Singer. 1975. “Summary Statement of the Asilomar Conference on Recombinant DNA Molecules”. Science New Series and Proc. Nat. Acad. Sci. 72 (6): 1981-1984 (June 1975).

The summary statement recommendations about the types of containment measures to be taken were:

Minimal containment	Follow the operating procedures recommended for clinical microbiological laboratories: no drinking, eating, or smoking in the laboratory; a wearing of laboratory coats in the work area; using cotton plug pipettes or mechanical pipetting devices: prompt disinfection of contaminated materials.
Low containment	All minimal procedures plus mechanical pipetting only; only directly involved laboratory personnel to have access to work areas; use of biological safety cabinets (laminar flow hoods) for procedures likely to produce aerosols; substitution of safer vectors and hosts as they become available.
Moderate containment	All preceding measures plus carrying out transfer operations within biological safety cabinets; gloves are worn during all handling of infectious materials; vacuum lines capturing lab exhaust air must be protected by filters; negative pressure to be maintained in limited access laboratories. Experiments to be done only with vectors and hosts that have been modified to impair their capacity to multiply outside laboratory.
High containment	All above measures plus isolation of laboratory work areas by airlocks; maintenance of a negative pressure environment in work areas; lab personnel must shower and change into protective laboratory clothing before entering the work area, and must change out of protective clothing and shower again after leaving the work area; laboratories must be fitted with exhaust systems equipped to incinerate exhaust air or pass it through HEPA filters. Experiments are to use rigorously tested vectors and hosts whose growth can be confined to the laboratory.

The Asilomar Conference summary statement also urged that risk experiments be undertaken to "monitor the escape or dissemination of cloning vehicles and their posts." These experiments were not intended to extend the frontiers of knowledge about genetic modification, but to understand more clearly how the organisms used in recombinant DNA research would act in the lab and in contact with natural environments if they spread outside the lab.

Overall, the Asilomar recommendations were based on what today would be regarded as a moderate version of the precautionary approach: scientists should proceed slowly and cautiously until they have proven a particular form of proposed research is safe. The scientists were keenly aware that accepting the recommendations meant deferring certain lines of work, and also accepting a need to spend money on upgrading their labs. Though the amount would depend on both the current configuration of their lab and the type of experiments they want to do. Modifying Paul Berg's lab for the rDNA work he wanted to do had cost tens of thousands of dollars, and it would need more upgrading to meet plasmid group suggestions regarding some of the experiments he wanted to do.

US Government Adoption of the Guidelines

As agreed, the Asilomar Conference Organizing Committee reported the results to the National Academy of Sciences, which then submitted them to the National Institutes of Health. It then reconvened the Recombinant DNA Advisory Committee to refine the Asilomar recommendations into usable guidelines.

Donald Fredrickson, who became Director of NIH in July 1975, later recalled his approach to developing formal guidelines from the Asilomar recommendations:

> As we went into the autumn of 1975, I had formed three convictions about the next steps in dealing with the tasks of the RAC. First, the public somehow must be consulted both before the guidelines were promulgated and consistently during their subsequent evolution. Second, the rules must remain flexible, admitting their constant revision as the evidential base changed. Finally, the NIH was the venue where these issues could best be handled.[21]

The first conviction put him at odds with some of the scientists, who were quite averse to having the general public involved. However, Fredrickson knew that in acceding to the scientists' desire for "guidelines, not regulations" to avoid the complexities of federal rule-making he was adopting an unusual approach likely to inspire adverse political comment unless it was managed carefully.[22] He regarded having some form of public input as essential to maintaining guidelines because the Administrative Procedure Act entrenched public comment as a requirement before issuing rules. The second and third convictions were more congenial to the scientists. They urged that the guidelines be open to revision as additional evidence about the danger or safety of particular forms of rDNA research became available, and much preferred dealing with NIH than with the agencies having regulatory powers like the Food and Drug Administration, the Department of Agriculture, or the Environmental Protection Agency.

Yet viewed from the political side, NIH did not look like the best possible place to develop the guidelines. It had no statutory authority to regulate anything and its reach extended only to its own employees or holders of NIH contracts or grants. It also lacked sufficient staff to monitor compliance; it had to rely very heavily on the institutional research committees established at universities and research centers. It could also be portrayed as having a conflict of interest since it was funding, and presumably interested in encouraging, rDNA research. However, it did have some advantages: significant in-house expertise in rDNA science, expertise far greater than possessed by any other federal agency, and credibility with the scientists, who were observing the moratorium but eager to resume work. Between 1977 and 1981 it also enjoyed strong support from Joseph Califano, President Carter's Secretary of Health, Education, and Welfare.

NIH began the process of developing guidelines by re-convening the RAC, now increased to 15 members, in February 1975. It was charged with translating the Asilomar statement into a set of workable guidelines. At its third meeting in June, the committee members present adopted a complete draft, and it circulated to other scientists for comment before the next scheduled meeting in December. Some of the missing members supported restrictive guidelines, and this affected the balance of the draft, which was widely

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[21] Donald S. Fredrickson, "The First Twenty-Five Years after Asilomar," Perspectives in Biology and Medicine 44.2 (2001), p. 172.

[22] Which are subject to the requirements of the Federal Code of Regulations, the Administrative Practice Act (APA), and the Federal Advisory Committee Act.

perceived as diluting the Asilomar recommendations. It drew a firestorm of criticism from individual scientists, including Paul Berg and others who had participated in the Asilomar Conference, and a joint letter of protest was signed by 48 biologists attending the1975 bacteriophage workshop at Cold Spring Harbor. The nature of the debate became public knowledge through stories in the Washington Post and the New York Times. Science later summarized the discussion with the headline "NIH Group Stirs Storm by Drafting Laxer Rules." A new subcommittee weighted towards more cautious scientists was commissioned to produce a new draft in November and bring it to the next RAC meeting. In December after several days of wrangling over competing formulations, the draft guidelines were tightened at the RAC's fourth meeting in La Jolla, California. This meeting, unlike the Woods Hole session, was attended not only by members of the committee but also by leading scientists (including Paul Berg, Sydney Brenner, Stanley Cohen and Maxine Singer), Emmett Barkley who was head of lab safety at the National Cancer Institute, observers from government agencies and pharmaceutical companies, and journalists.

Fredrickson decided that the state of public concern about rDNA hazards required adding more public participation and comment to the process. This was accomplished by reviving a dormant NIH Director's Advisory Committee and giving it 20 members. Four were scientists familiar with molecular biology, including Robert Sinsheimer, Chair of the Biology Department at the California Institute of Technology and a well-known scientist critical of rDNA research. Other members included two college students, the provost of MIT, the Dean of a west coast medical school, a medical doctor, two ethicists, the President of the National Academy of Sciences, President Lyndon Johnson's chief consumer advocate, and Judge David Bazelon of the US Court of Appeals for the Third Circuit.[23] Meetings of the Director's Advisory Committee were announced in advance and public participation was encouraged by issuing invitations to a wide range of issue-oriented organizations like Friends of the Earth, the League of Women Voters, and the Sierra Club.

The pattern of the February meeting became the template for meetings of the Director's Advisory Committee in 1976-78 and then of the enlarged Recombinant DNA Advisory Committee starting in 1979. Each multi-day meeting included time for public comment as well as discussion by members of the committee, a summary of the proceedings would be published in the Federal Register, a period for additional comment from members of the public followed, with each comment received answered in a Director's review.

After being warned by the Department of Health, Education, and Welfare's General Counsel that NIH lacked authority to make "rules", as that term is defined in US Federal Law, the successive versions of the guidelines were communicated to the public through "notices of proposed rule-making" published in the Federal Register.[24] NIH also secured its role vis-à-vis other federal agencies by getting President Ford to agree to creation of a Federal Interagency Committee on Recombinant DNA Research and designating NIH as the presiding agency. Later HEW Secretary Califano simultaneously headed off other potential challenges and extended the reach of NIH Guidelines by instructing the Food and Drug Administration to announce it would only approve the sale of products created through use of rDNA when the NIH Guidelines had been followed during their development.

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[23] Fredrickson 2001, p. 173. Appendix C lists the members.

[24]Fredrickson, 2001, p. 174. Today NIH also posts the Guidelines on its website. Accessed June 15, 2010. http://oba.od.nih.gov/rdna/nih_guidelines_oba.html.

All of this took time, and also drew NIH into unfamiliar surroundings. As the process of developing the guidelines wore on, NIH faced pressures from two sides. As Fredrickson recalled,

> Hans Settin warned that "The scientists are close to mutiny waiting for the Guidelines." The NIH General Counsel and the environmental community warned of litigation if the Guidelines were promulgated without an Environmental Impact Statement (EIS).[25]

NIH averted revolt from the scientists by issuing the first version of the Guidelines in June 1976 and sought to address the lawyers and environmentalists by accelerating the EIS process and issuing the draft EIS in August (the final, which could not be issued until a period of public consultation on the draft, appeared in October 1977).

While NIH was developing these procedures, the wider public debate about the desirability and safety of rDNA research continued to rage in the press, in Congress, and in cities home to major research institutions. This had begun in earnest after the Asilomar Conference had been noted in the press. The Asilomar organizers argued among themselves about whether and how to include journalists. They eventually settled on inviting 16 journalists who specialized in science reporting on the condition that they stay for the whole conference and wait until it was over before sending anything to their editors.[26] The articles that appeared afterwards conveyed the intensity of disagreement expressed at the conference as well as the final recommendations. The more general press coverage continued to highlight the risks and the lack of knowledge about the impact of rDNA on natural systems but also began pointing out the potential benefits. Several bills for regulating rDNA research were introduced in Congress, but none was passed, partly because of disagreements among members of Congress and partly because of lobbying by scientists seeking to keep the subject within NIH purview. In 1977, the City of Cambridge, Massachusetts held extensive public hearings on rDNA research, led mainly by an appointed Cambridge Experimentation Review Board consisting of 7 citizens chosen from various parts of the city, one medical doctor, and the City Commissioner of Health and Hospitals. The process culminated in adoption of an ordinance imposing additional containment requirements on rDNA labs built in the city and provision for health monitoring to ensure public safety. Other cities also adopted ordinances, but in the main these added to rather than ignore the NIH Guidelines.[27]

Once the initial Guidelines were issued, the rule-making task shifted from marking out new routines to adjusting routines to new conditions. This allowed some consolidation of tasks by abandoning the RAC-Director's Advisory Committee structure for a single-committee structure consisting of an enlarged RAC of 25 rather than 20 members, of whom 1/3 were to be non-scientists. The enlarged RAC became the body reviewing new versions of the Guidelines and also advising on other questions relating to basic and clinical research involving recombinant DNA.[28]

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[25] Fredrickson, 2001, p. 174.

[26] Alexander M. Capron and Renie Schapiro, "Remember Asilomar? Reexamining Science's Ethical and Social Responsibility," Perspectives in Biology and Medicine 44.2 (2001), p. 164.

[27] Local initiatives summarized in Sheldon Krimsky. 1979. "A comparative view of state and municipal laws regulating the use of recombinant DNA molecules technology," Recombinant DNA Technical Bulletin 2(3): 121-125 (November).

[28] Information on its current membership and activities is available on the NIH website at http://oba.od.nih.gov/rdna_rac/rac_about.html (accessed 21 June 2010).

Scientists' own uncertainty about the hazards coupled with continuing public worry or outright opposition to rDNA research remained high enough to trigger a series of additional scientific workshops on the safety of rDNA research in 1977 and 1978. These reviewed experiments and generally concluded that the worst fears of "super pathogens" of "super hybrid species would not materialize. These judgments were facilitated and put on firmer ground by considerable work following up on Brenner's suggestion to "disarm" plasmids, phages, and bacteria by breeding strains unable to live or reproduce outside labs.[29] Experiments with rDNA work resumed after adoption of the Guidelines in mid 1976 and proceeded without any incidents of materials escaping from labs. By 1980, media reporting on rDNA research was shifting from disaster scenarios to the potential for improving treatment of disease or breeding of plants with rDNA. In light of these findings and changes, the guidelines were revised to permit more forms of experiment or to reclassify existing forms of experiment into lower risk categories.

The Asilomar Conference in Retrospect

There is broad agreement that the biological scientists who proposed suspending experiments with rDNA while the actual degree of risk posed by rDNA experiments were unusually forward-looking in their approach to new scientific possibilities. Rather than proceed at full speed and find out the characteristics and extent of danger after having done a considerable number of experiments, they put their own research aside while attempting to analyze the negative effects it might cause. Even after the moratorium was lifted, they agreed that certain regulations limiting scientists' choice of experiments, limiting their choice of organisms to use in experiments, and mandating lab and lab worker safety were still needed.

As they moved from the abstract categories of the Asilomar summary recommendations to the more complex activities going into the research, the leading rDNA researchers realized that they had to find a middle ground between two sets of challengers within the scientific community. They had to persuade scientists who strongly opposed any restrictions on choice of projects and research methods that some level of regulation was necessary to maintaining enough public confidence that the scientific community would be allowed to proceed with research and formulate the guidelines under which it occurred. They also had to persuade scientists who thought research should not continue until broader issues about the uses of rDNA technology had been addressed to pursue those interests in other forums lest disagreements on those issues divert the effort to develop guidelines on experimentation and leave regulatory decisions to Congress or to government agencies likely to respond to mounting public fear of rDNA research with sweeping restrictions that would be difficult to get changed later.

For some observers, the choices leading to the Asilomar Conference and its discussions provide a model of scientific leadership in public debates that should be emulated. In this view, the Asilomar process provides a way that scientists as a group can balance the traditional scientific values of freedom of inquiry with the contemporary need to consider the impact of developing new knowledge that will have significant implications for society once it is disseminated and used to develop real world applications.[30]

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[29] Rogers 1977, p. 66 says Brenner used the "disarm" analogy at Asilomar.

[30] Carl Mitcham. 1987. "Responsibility and technology: The expanding relationship," in Paul T. Durbin, ed. Technology and Responsibility (Dordrecht, Neth: Reidel Publishing.)

For others, the model is inadequate. One set of critics maintain that it was inadequate even at the time because the scientists largely excluded non-scientists from their discussions and used the process to preserve traditions of scientific self-governance at the expense of democratic values and the public good.[31] Contemporaneous critics believed scientists should have considered at least three broader concerns when deciding whether to pursue any, some, or all rDNA research:

1. Recombinant DNA as technological fix. This debate reaches beyond the safety of particular forms of rDNA experimentation to ask whether rDNA technologies should be developed, either because the risks outweigh the benefits or because the benefits (for example, an increase in insulin for treating diabetes) could be achieved by other means (with adult-onset diabetes, getting people to improve their diets, exercise more, and avoid obesity) involving less reliance on new technologies or products. These arguments rested on a broader socio-political critique maintaining that seeking technological fixes diverts attention from the need to change society and/or individual behavior.

2. Recombinant DNA would allow humans to alter the course of evolution. This debate was particularly resonant with nonscientists worried about rDNA work on religious and ethical grounds. In its more scientific versions, the argument proceeded from contrasting natural evolution, which occurs in complex interactions among species and habitats over long periods, with the artificial method of genetic modification to concluding that genetic modification is very likely to have harmful consequences because it disrupts the balances inherent in natural evolutionary processes. As expressed at the time, it was also an early version of calls for adopting a strong reading of the precautionary principle and not proceeding until the safety of activity had been proven.

3. Use of DNA recombination techniques for evil purposes. This debate was an expression of the rising ambivalence about knowledge that could lead to new technologies which marked the latter half of the 20th century. Those concerned about averting harm suggested that knowledge that could be turned to intentionally harmful uses should not be developed. Yet the record of abstention from new technologies once their possibilities have been suggested is very weak, particularly as potentially beneficial uses come into view. At that point debate shifts from averting harm by restricting knowledge to averting harm by restricting uses.

Another set of critics maintain that though the model was adequate in the conditions prevailing in the early 1970s it is either inadequate or would not work today. The reasons provided to explain the difference vary, ranging from increases in the size of the scientific community, to the greater prominence of commercial interests,[32] to doubt that scientists as a group can and will adequately consider the public good when

[31] Roughly contemporaneous expressions of this view included. Later expressions include Susan Wright. 1994. Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972-1982 (Chicago: University of Chicago Press); Hong Lim Oei. 1997. Genes and Politics: The Recombinant DNA Debate (Burke, VA: Chatelaine Press)

[32] E.g., Alexander M. Capron and Renie Schapiro, Remember Asilomar? Reexamining Science's Ethical and Social Responsibility," Perspectives in Biology and Medicine 44.2 (2001) 168.

deciding what lines of research to undertake,[33] to reduced public willingness to defer to expert opinion on matters of risk.[34]

Some commentators believe the Asilomar approach might work today in certain circumstances—when the area of research is truly new, no commercial interests in developing applications of the research have emerged, and the number of scientists whose research would be affected by restrictions is sufficiently small that bans or moratoria could be effective.

In light of later European restrictions on use of rDNA technology in foods, feeds, and plants, it is intriguing to note that during the 1970s only the United Kingdom had similarly lengthy and explicit debates about whether to conduct rDNA research and how to regulate it. These debates had begun a bit before the US ones,[35] also included disputes about the adequacy of proposed guidelines,[36] and concluded with issuance of more elaborate guidelines in the Report of the Working Party on the Practice of Genetic Manipulation.[37] The British guidelines differed from the US ones in two ways: a) the UK Health and Safety Commission had legal authority to enforce compliance with the Working Party Guidelines on industrial, government, and university labs alike, and b) classification of the hazard level of experiments would be done on a case-by-case basis by a new Genetic Manipulation Advisory Group. Australia adopted guidelines similar to the US ones; the situation in Western Europe was varied enough to encourage tales of European researchers moving their work to places where local law allowed them to do the particular experiments they had in mind until European governments largely converged on using the British standards.[38] The Soviet Union and Eastern European countries did not adopt any laws or explicit guidelines, though some Soviet scientists did attend the Asilomar Conference.

Any assessment of the worth of the Asilomar model for scientific assessment of risks depends on the assessor's conception of what the conferences intended to accomplish. It is an inadequate model for social decisions about whether to proceed with the development or particular applications of a new technology, as many of the participants themselves acknowledged. Today there are a host of ideas about how to make such decisions, ranging from leave them to the institutions of representative democracy to involve citizens directly through such processes as deliberative polling, consensus conferences, scenario workshops,

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[33] E.g., Susan Wright. 1994. Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972-1982 (Chicago: University of Chicago Press); Hong Lim Oei. 1997. Genes and Politics: The Recombinant DNA Debate (Burke, VA: Chatelaine Press).

[34] E.g., Alan N. Schechter and Robert L. Perlman. "Editors' Introduction to the Symposium on the 25th Anniversary of the Asilomar Conference," Perspectives in Biology and Medicine 44.2 (2001) 159.

[35] Report of the Working Party on the Experimental Manipulation of the Genetic Composition of Micro-Organisms (Ashby Report). Presented to Parliament by the Secretary of State for Education and Science by Command of Her Majesty, January 1975 (London: Her Majesty's Stationery Office, 1975).

[36] Recommendations in the January 1975 Ashby Report were considered too weak by many. See Bernard Dixon. 1975. "Not good enough." New Scientist 65: 186 (23 January 1975).

[37] Report of the Working Party on the Practice of Genetic Manipulation (Williams Report). August 1976.

[38] Noted by Rogers 1977, p. 203.

citizen juries, or direct initiatives.[39] What they have in common is a desire to have regular citizens, not technical experts, commercial interests, or social elites at the center of decision-making.

The Asilomar model is adequate for organizing risk assessment when an area of scientific inquiry or a technology is so new that there is little or no experience to be drawn in making the probabilistic estimates of risk on which benefit-cost analysis depends. Even if at some level Robert Oppenheimer's summary of the situation regarding atomic energy in 1944-45 – "There are no experts. The field is too new."[40] – is correct, that does not mean everyone is equally capable of helping discern the likelihood of danger and the extent of its impact. Processes of collective expert consideration, joined with suspending work if that seems necessary, are the only way to move even partly from the realm of uncertainty, where dangers and benefits can be conceived only in broad outline, to the realm of risk where pathways to danger can be identified and measures taken to reduce either or both the likelihood or the extent of harmful effects.

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[39] Discussions of these methods include Ida-Elizabeth Andersen and Birgit Jaeger. 1990. "Scenario workshops and consensus conferences: Towards more democratic decision-making," Science and Public Policy 26 (5): 331-340; Johan Schot. 2001. "Constructive technology assessment as reflexive technology politics," in Technology and Ethics: A European Quest for Responsible Engineering (Leuven, Belgium: Peters); John Gastil and Peter Levine, eds. 2005. The Deliberative Democracy Handbook: Strategies for Effective Civic Engagement in the Twenty-First Century (San Francisco: Jossey-Bass) James L. Creighton. 2005. The Public Participation Handbook: Making Better Decisions through Citizen Involvement (San Francisco: Jossey-Bass); and James Fishkin's Deliberative Polling process, described at http://cdd.stanford.edu/polls/docs/summary/ (accessed 21 June 2010).

[40] Quoted in Rogers 1977, p. 104.