Photos: Andrew A. Stern/National Academy of Sciences

Conference organizers drafting the recommendations.

Lessons from Asilomar

Ten years after the historic conference on the risks of gene-splicing research, scientists look back with a mixture of pride, disappointment and embarrassment

By JULIE ANN MILLER

Among redwoods, Monterey pines and migrating monarch butterflies, 140 molecular biologists spent four long and intense days a decade ago. They had congregated in a building that was once a chapel to ponder and debate the ethics of using a technique that had recently burst upon their field. Today no one questions the power of recombinant DNA technology — often called gene splicing — that was then their focus. It allows the cutting, rearranging and reproduction (or cloning) of DNA, the genetic material.

Indeed, molecular biologists now jokingly refer to the pre-1975 days of their research as "B.C." or "before cloning," implying that biology before gene splicing was primitive and clumsy. The gene-splicing technique has been widely and enthusiastically embraced. Quite simply, it has revolutionized biology.

But what of the ethical concerns that dogged the early progress of the method? In new guises, they continue to hound the field today.

The meeting in February 1975 at the Asilomar Conference Center in Pacific Grove, Calif., was unique in the history of biology. The scientists convened not to describe their scientific advances but to assess potential risks of the new technique and to suggest limitations on its use in research. The foremost risk then imagined was that a novel microorganism might be created experimentally — and released accidentally — to cause an epidemic of cancer or some new and incurable disease. The way the scientists dealt with such hypothetical risks at that meeting continues to affect the conduct of biological research today.

The story behind the Asilomar conference actually begins in June 1973 at a closed scientific meeting in New Hampshire. There, participants described the development of a simple method for combining segments of DNA taken from unrelated species. In an unusual action, scientists attending that meeting voted to send a letter of concern to the National Academy of Sciences.

The brief letter, which was also published in SCIENCE, said that hybrid DNA molecules produced by the new technique might prove hazardous to laboratory workers and to the public. "Although no hazard has yet been established, prudence suggests that the potential hazard be seriously considered," the letter stated.

A second letter concerning such DNA research was published a year later in both SCIENCE and NATURE. Subsequently called the "moratorium letter," it was written by an academy-appointed committee of leading molecular biologists, including Paul Berg of Stanford University and James D. Watson of Cold Spring Harbor (N.Y.) Laboratory. This letter called for scientists around the world to "voluntarily defer" certain types of recombinant DNA experiments. It also recommended that an international gathering of scientists discuss ways to deal with the "potentially hazardous DNA molecules."

Most of the international meeting — the Asilomar conference — was devoted to describing progress in molecular biology research. "The first days were purely scientific showing-off, in other words a typical scientific meeting," recalls one participant. Only on the last morning did the focus shift to risks and how to deal with them.

The meeting's organizers had spent all the preceding night drafting new research guidelines. They recommended that the "moratorium" be lifted and replaced with a scale of special safety procedures corresponding to a scale of conjectural hazards associated with different types of recombinant DNA experiments. Some scientists, including Watson, objected to the statement. But the majority at the meeting agreed, or at least did not vocally disagree, to the committee's recommendations. The report was eventually submitted to the National Academy and published in SCIENCE in June 1975. It became the basis of the National Institutes of Health (NIH) guidelines that have governed gene-splicing research throughout the United States since 1976.

Called on to reminisce about the Asilomar meeting, molecular biologists now express a variety of views about the event, the concerns that gave rise to it and its impact on the history of science. There is wide agreement, however, about the power of gene splicing.

"The lesson of Asilomar is that, even having the imposed constraints, progress in the field has been stupendous," Berg, the organizer of the Asilomar meeting, told SCIENCE NEWS in a recent interview. "I am overwhelmed by how broadly this development has permeated science . . . [and] at the sophistication and level of sheer versatility and elegance of the way [biology is] being done."

Jonathan King of Massachusetts Institute of Technology concurs that "it enormously speeded up acquisition of knowledge and of new products in the market." Although he uses the techniques in his own research and chairs one of the NIH

committees that fund gene-splicing research, King has steadfastly voiced strong concern about potential hazards of scientist-modified microorganisms.

From the other end of the spectrum Waclaw Szybalski of the University of Wisconsin at Madison says, "We've invented fire. The sky's the limit." Szybalski has consistently opposed regulation of recombinant DNA research.

Before the development of gene-splicing techniques, almost nothing was known about the organization and function of DNA in eukaryotes — organisms, including animals and plants, that are more complex than bacteria. Such research has provided many surprises. "The structure of genes is more complicated than anyone had thought," Berg says. For example, there was the "shocking" discovery that most plant and animal genes are divided into several segments separated by regions of DNA whose function is still unknown (SN: 10/1/77, p. 214).

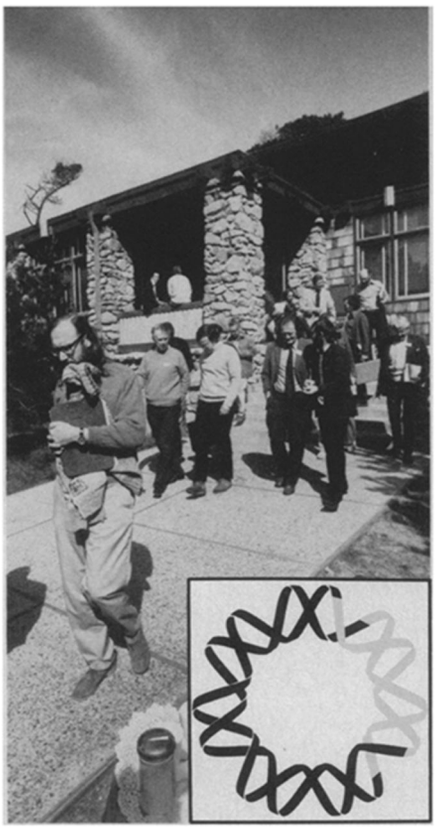
Another surprise was that DNA segments regulating the activity of a gene do not need to be adjacent to it, but may act across great distances (SN: 2/26/83, p. 139). Other unexpected findings were the rearrangement of parts of certain genes during development (SN: 12/11/76, p. 372), the existence of families of genes (SN: 12/20 & 27/80, p. 396) and the presence of many movable elements in DNA (SN: 4/28/84, p. 264).

Gene splicing's potential power and wide usage worried some biologists in 1975. "All our predictions came true," says King. A group of biologists predicted, for example, that recombinant DNA techniques would come to be used in industrial production as well as in research and that scientists would design organisms to be introduced into the environment. Each of these predictions was once deemed science fiction by other scientists, according to King. He now says, "History has proved us correct."

"The application of these techniques is going to continue to open up new horizons," King says. "It is precisely because of this power and productivity that regulation and public oversight functions must continue to expand."

Nonetheless, the concerns of most biologists about hazards of recombinant DNA research have lessened over the years of use. Watson, as early as the Asilomar meeting, had proposed that the moratorium be lifted and no special precautions or guidelines be imposed. He repudiated his signing of the moratorium letter: "Scientifically, I was a nut," he said in 1978. "There is no evidence at all that recombinant DNA poses the slightest danger."

Szybalski agrees. "We should have said clearly [at Asilomar] there is no practical danger. It was clear in my mind and in the minds of people who knew anything about biology in general."



Asilomar Conference Center. Inset: The plasmid, or ring of DNA, has come to symbolize recombinant DNA research.

But Berg says that when the recombinant DNA techniques emerged, scientists were uncertain about safety questions. "I couldn't say there was zero risk," he recalls. A sense of personal responsibility motivated him to raise the safety issue, he says, explaining that even if he could accept a small chance of danger, he realized that the people working around him might not be so "gung ho." Recalling a meeting in 1973 where scientists considered the potential risks in working with tumor viruses, he says there was already a feeling that "some things might be dangerous. ... At Asilomar we agreed that we didn't know enough to make a judgment [on the safety of gene splicing], and 95 percent of us agreed that it would be better to go slow."

Many scientists have objected over the decade to the way the Asilomar meeting was run. King says that the participants, who were all specially invited, did not include people with "key sectors of expertise," such as epidemiology or environmental science. Moreover, most of the participants' own research would benefit directly from the recombinant DNA techniques.

Szybalski recalls, "I thought it was one of the most strange events. It was generated by scientists and conducted by scientists without paying much attention to the scientific facts at that time." To emphasize this oddity, Szybalski cites the caustic words of DeWitt Stetton, former deputy director for science at NIH. Stetton said the meeting had "many elements of a religious revival meeting. I heard several colleagues declaim against sin, I heard others admit to having sinned, and there was a general feeling that we should all go forth and sin no more.... We were all, in effect, led down to the river to be baptized."

"It was a reflection of the Vietnam era and earlier history," Szybalski says. "Physicists were guilty of the atomic bomb, and chemists were guilty of napalm. Biologists were trying very hard to be guilty of something. And they tried to show that they were better than the physicists and chemists.... It was an ego trip at the beginning."

On the mechanics of the meeting, Szybalski says, "It was the worst democracy-in-action." The important decisions, he says, were made at the end of the meeting and the participants were allowed only to approve or reject, not to thoroughly discuss, the proposals. "All of us were tired," he says. "It was the end, and we wanted to go home.... Now Asilomar is for me an open sore. I'm still embarrassed to have participated."

An admitted purpose of the meeting, aside from humanitarian concerns, was to prevent nonscientists from imposing limits on biological research. Berg says the conference provided necessary "groundwork" for continuing the research. "If we had tried to brazen it through, we would have been prevented, and 10 years later we would still be battling to get restrictive legislation lifted," he says. "My guess is that had we not taken the initiative, [others] would have been effective in creating a more restrictive atmosphere through legislation and psychology."

However, some scientists feel that the public should have played a greater role in deciding how to regulate gene-splicing research. "At least," King says, "the question of public oversight was raised and entered into the debate before being beaten down."

But others, believing the technique has no safety risks, feel that it would have been better to keep the public in the dark. "Nothing would have happened if the situation had not been created by Berg," Szybalski says. He points to other research techniques using X-rays or chemicals for making random, rather than specific, changes in the genes of bacteria. Hypothetical outcomes of these techniques could have been construed as far worse than those more recently imagined for recombinant DNA research. But the techniques were not called to public attention, there was no legislation, the methods were used to create new antibiotics that saved many lives and no special dangers were ever forthcoming. This should have been the situation for recombinant DNA also, Szybalski asserts. Instead, the public concluded the technique must be dangerous, because scientists themselves set up restrictions governing its use.

Many scientists believe the proposals

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tured TCE is lost — disperses to soil and water over time.

Coauthors Yoram Cohen and Patrick A. Ryan of the University of California at Los Angeles (UCLA) constructed a mathematical model to represent air, soil, water, sediment and fish, then looked at how TCE distributes itself into each of these. If TCE stayed in the air, it would degrade in sunlight as all chlorinated organic compounds do (though some take longer than others). But the UCLA model shows that before all the TCE can be broken down, it settles into soils and sediments, where it is more stable.

The final TCE concentrations predicted by the model reasonably correspond, say the authors, to actual levels found in the environment. And because the model considers shifting pollutants over time, it can be used to point out to policymakers which chemicals pose the most threat and where.

"This is a tool for determining pollutant pathways and where the environmental hot spots are," says Cohen. A toxic chemical may not be an air problem if it breaks down quickly, but it can become a serious land problem if it accumulates in the agricultural topsoil. Cohen expects multimedia modeling to be useful in screening new chemicals as well as existing ones. Manufacturers develop more than 1,000 new chemicals each year.

Cohen conducts his research at the National Center for Intermedia Transport Research, an EPA-funded center at UCLA. In the young field of cross-media research, it is the only organized academic research group that studies the mechanisms of pollutant transport through the whole environment. The group of eight scientists and engineers is concentrating on organic pollutants and their behavior at media boundaries, as well as their flow and accumulation in the environment.

Tracking and transport studies look at pollutants once they are released into the environment. But the ultimate cross-media control, according to many speakers at the Washington conference, is to catch pollutants at their sources. Source reduction is going on, says Richard E. Heckert of E. I. du Pont de Nemours & Co. in Wilmington, Del. Industries are practicing "preventive environmental medicine," he says, by designing manufacturing processes to avoid or reduce waste, by recycling some wastes as fuel and by considering potential environmental impacts before building new plants.

Still, four-fifths of the 118 million metric tons (dry weight) of sludge generated annually in the United States comes from industries. Their wastes, along with the remains of sewage and water treatments, make up a morass of organic and inorganic chemicals, heavy metals, viruses and bacteria. Land receives the bulk of this waste, which is intended to be securely contained. But its more toxic and persistent ingredients often make their way into soils and groundwater as well as into the air.

Conference speakers pointed out the need for an umbrella policy to deal with the seemingly disparate problems of hazardous sludge, contaminated groundwater and acid rain, all of which affect mixed media. The basic ideas of integrated environmental control are not new — the EPA itself was formed in the ecology-minded mood of the late 1960s. But medium-specific laws, bureaucratic divisions, strict scientific specialties and even environmental groups that lobby separately for clean air, clean water and clean land have hampered the development of an integrated policy. "The lack of data hamstrings us all," says Glenn Paulson of the National Audubon Society in New York, but "we lack conceptual, intellectual tools, too" for an integrated control.

Resurgent interest in the cross-media problem may provide a few more tools that work within the existing framework. There is enough "wiggle room" in current laws to allow cross-media considerations at least at the state or local level, according to Ernest Abbott of EPA's policy office. But in the long run, says J. Clarence Davies of the Conservation Foundation, the media-oriented laws will at least have to be modified for an integrated approach. □

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from the Asilomar meeting slowed the initial stages of gene-splicing research, outlawing certain experiments and making others difficult or too expensive. In addition, hours and hours of scientists' time were spent drafting guidelines, applying for permission to perform experiments and appearing before legislative committees. Some scientists, such as Szybalski, refrained from doing any recombinant DNA experiments because they so strongly objected to being regulated.

Over the years the NIH guidelines have been repeatedly revised, easing the safety restrictions on gene-splicing research. "Much blood, sweat and tears went into changing the regulations," Szybalski says. "The people who undid all that damage should get a monument."

Berg, too, was dismayed at how much energy and time was consumed by the public debate in the years following the Asilomar conference. However, he believes that the overall effect was positive: "Now, 10 years later, no one could convince me that [guidelines arising from the Asilomar conference] impeded research. It only stopped things that we couldn't yet do anyway."

Has there been any ill effect on health or on the environment? Most scientists are convinced there has not been the slightest harmful outcome in the decade of widespread gene-splicing research. But

Paul Berg

King says he is disappointed that there is no program to monitor possible problems. "If no one is collecting data, we can make no statement," he says.

Berg's greatest disappointment is that the experience gained in dealing with the recombinant DNA issue has not established any clear precedent for handling other potentially controversial new technologies. "In a sense, we went through the whole exercise...but left no process in place. If new concerns arise, it would be the same thing all over again — a process as primitive and as inefficient as before."

Today recombinant DNA controversies are still in the news. For instance, guidelines for the first research into clinical uses of gene splicing were recently recommended (SN: 2/2/85, p. 71). Harold Varmus of the University of California at San Francisco, who helped draft them, says, "The lesson of Asilomar should be transmitted to the gene-therapy people. That lesson is: Don't get bogged down in too many regulations."

Yet the absence of laws regarding recombinant DNA research has not granted gene splicers immunity from legal problems. Court decisions now block the first experiments involving deliberate release of genetically engineered microorganisms into the environment (SN: 12/22 & 29/84, p. 397). But even the biologists who are frankly upset by this obstruction of recombinant DNA research do not propose a return to Asilomar as a way of solving the problems they now face.

"The Asilomar conference was really a child of the '60s and early '70s, an innocent time for everybody," says Janet Hopson, who covered the meeting for SCIENCE NEWS. "Things will never be like that again." □