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23. D. S. Landes, *The Unbound Prometheus; Technological Change and Industrial Development in Western Europe from 1750 to the Present* (Cambridge Univ. Press, Cambridge, 1969), pp. 277–278.
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25. See P. Temin, *J. Econ. Hist.* **26**, 188 (1966); V. S. Clark, *History of Manufactures in the United States* (Carnegie Institution of Washington, Washington, D.C., 1929), vol. 1, p. 409.
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27. H. J. Barnett and C. Morse, *Scarcity and Growth; The Economics of Natural Resource Availability* (Johns Hopkins Press, Baltimore, Md., 1963), p. 10. See also Passell and Ross (*7*, p. 32), Solow (*11*, pp. 44–48), and Rosenberg (*18*, pp. 18–23).
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NEWS AND COMMENT

Genetics: Conference Sets Strict Controls to Replace Moratorium

Pacific Grove, California. In a meeting that will possibly rate at least a footnote in the history of science, an international group of biologists has voted in principle to lift the voluntary moratorium imposed last July on a new technique of genetic manipulation that involves constructing hybrid molecules of DNA. But the moratorium is to be replaced with safety conditions so stringent that for many experiments it will effectively remain in force for a period at least of months. The conference also recorded its wish that the most hazardous category of experiments made possible by the technique should not be performed under any circumstances whatsoever.

Like the moratorium that preceded it, the conference's statement has the power of moral censure only, but the guidelines it proposes will probably be followed closely by the national bodies in each country responsible for framing the relevant regulations.

Just as the moratorium seems to be unprecedented in the history of science, the action of the conference is a rare, if not unique, example of safety precautions being imposed on a technical development before, instead of after, the first occurrence of the hazard being guarded against.

The conference's decisions were reached in the explicit awareness that science no longer enjoys the automatic favor of governments and society, and that if the scientists present failed to regulate themselves in an evidently disinterested manner, others would do so for them. As it happens, the control measures proposed by the conference are considerably stricter than many of those active in the field believed necessary and furthermore include a quite novel safety feature stipulating that the organisms involved in the experiments shall be biologically incapable of surviving outside the laboratory.

The conference can also be seen as a personal triumph for its committee chairman, Paul Berg of the Stanford University Medical Center. It was Berg who first had scruples about the possible hazards of the technique when he developed an early version of it 2 years ago. It was he to whom the National Academy of Sciences (NAS) turned when the approaching dangers of the technique became evident. With a group of colleagues, Berg decided last July that the issue should be put before an international conference but, to prevent dangerous molecules being constructed in the interim, the group invited scientists throughout the world to join them in voluntarily deferring certain experiments involving the technique (see *Science,* 26 July 1974, p. 332).

It says much for the moral authority of Berg's group that, as far as is known, the moratorium has been observed worldwide. Although safety regulations are not a subject of intense interest to many scientists, almost everyone invited attended the meeting held last month at the Asilomar conference center. The committee was able to persuade a group of 140 competitive and strong willed individuals, most of them quite unaccustomed to being told how to do their experiments, to reach a remarkable degree of consensus on how the problem should be resolved.

The decision reached on 27 February at Asilomar will be far reaching because it governs a technique which is widely expected both to revolutionize the study of molecular biology and to bring some of the wilder fantasies of genetic engineers into the realm of the possible. The basis of the technique is a newly discovered class of enzymes which possess two special properties. They cleave DNA into segments of manageable size, a few genes or so in length, and they make cuts which chemically have "sticky ends," enabling a segment from one molecule to be annealed with that of another, even if the two molecules come from different species.

In fact, most foreseeable exploitations of the technique involve joining the DNA of different species into a single hybrid molecule, of which one part is the gene or genes to be studied, and the other is a vector—often the DNA of a virus—which has the ability to enter a cell and get itself (and its hybrid partner) replicated by the cell's genetic machinery.

These hybrid molecules look as if they will render tractable many problems in biology which people have long despaired of solving with present techniques. They are also the stuff of such science fiction scenarios as inserting nitrogen-fixing genes into plants and programming bacteria to synthesize insulin and other products of human genes, to cite but two of the possibilities mentioned at the conference.

The danger is that such manipulations may create novel arrangements of genetic material which have not occurred in evolution, with results that are impossible to predict. A likely host for many hybrid DNA's will be the standard laboratory organism, *Escherichia coli,* a common inhabitant of the human gut and nose. In the worse conceivable case, an *E. coli* bacterium infected by a virus which some manipulation had unintentionally rendered pathogenic might escape from the laboratory, infect the population outside, and set off a human epidemic of perhaps myxomatosis-like proportions. The incidence of laboratory acquired infections—5000 in the last 30 years, a third of them in laboratories with special containment facilities—suggests that the eventual escape of such an organism, if created, could probably be expected.

Few scientists acquainted with the power of the new technique would lightly forgo its use, yet how could the public be informed the moratorium was at an end when the unknown hazards that caused it to be invoked in the first place were just as unknown as before? This was the crux of the problem that the delegates at the Asilomar conference debated for 3½ days of concentrated and occasionally dramatic sessions. The 53 foreign delegates included scientists mostly from Europe and Russia. The Russians said not a word until the very end. The Europeans spoke very little except for the English, who had left a confused situation at home. The British Medical Research Council (MRC) had in July, by confidential letter to its laboratory directors, effectively banned all the experiments placed under voluntary embargo by the Berg committee. But a government-sponsored group of scientists known as the Ashby committee concluded in December that the technique was too important to curb and that the experiments should proceed under certain safety conditions. (These were considerably more flexible than the conditions the Asilomar conference was to recommend.) The British government has not yet acted on its committee's suggestions, and there is concern that a recent fatal accident in handling smallpox virus at the London School of Hygiene and Tropical Medicine may lead bureaucratic minds to wonder if scientists' ideas about laboratory safety are safe enough.

The English delegates were thus well schooled in the political aspects of the problem. One of them, Sydney Brenner (MCR Laboratory of Molecular Biology), was perhaps the major influence on the conference after Berg. A member of the conference organizing committee,* Brenner had the knack of intervening at crucial stages in the debate and holding the audience spellbound with arguments of urgent lucidity in favor of drawing up safety procedures so evidently tight that no one could reasonably accuse the scientific community of self serving. (One opponent complained privately that Brenner intimidated people.) He also was the leading advocate of developing biological safety barriers for the technique —a feature that lies at the heart of the conference's solution to its dilemma. In common with Berg and David Baltimore (MIT), Brenner always seemed to be more conscious than other delegates of the outside world looking in and gauging risks and behavior with a different yardstick. While some people were for drawing up safety guidelines that would minimize the risk, Brenner's definition of a successful guideline was one that, in the future, would be revised downward.

The organizing committee's chief opponents were James Watson (Cold Spring Harbor) and Joshua Lederberg (Stanford University Medical Center). Like a pair of *enfants terribles,* the two Nobel laureates were constantly discovering holes in the committee's positions and—although there seemed to be no concerted campaign—breaking the ice for the faction among the younger scientists who were eager to get the moratorium lifted on the easiest terms feasible.

The conference, held in a small chapel a few yards from the Pacific Ocean, was opened with a statement by Baltimore. He reminded people that if they failed to come to a consensus, if they split along lines he could easily

* The members of the organizing committee were Paul Berg, chairman (Stanford University Medical Center), David Baltimore (MIT), Sydney Brenner (MRC Laboratory of Molecular Biology), Niels K. Jerne (Basel Institute for Immunology, Switzerland), Richard O. Roblin (Harvard Medical School), and Maxine F. Singer (National Institutes of Health). Berg and Baltimore were also members of the ad hoc NAS committte that invoked the moratorium. The title of the meeting was the International Conference on Recombinant DNA Molecules.

imagine, there was no one else to appeal to, and the conference would have failed in its duty. "How was the consensus to be determined?" someone inquired. "The procedures by which the consensus will be determined will be largely determined by the extent of the concensus," was the unyielding reply.

The microbiological presentations which followed confirmed that K12, the common laboratory strain of *E. coli*, may be enfeebled from years of being kicked around genetically, but it can still survive long enough in the human gut to exchange genetic material (specifically, the extrachromosomal elements known as plasmids) with other bacteria in the region. This established a crucial link in the worst case scenario for a laboratory accident. It also pointed to caution in the use of plasmids (the major candidates along with viruses) for the vector part of hybrid molecules.

Benefits Look Larger than Risks

The conference next heard from Harold Green, one of its few outsiders. A Washington lawyer interested in public policy aspects of science, Green's chief point was the warning that at the inception of any new technology, the benefits, which are tangible and near at hand, are often permitted to outweigh the more distant seeming risks. Two examples which surfaced later in the meeting, though Green did not specifically cite them, were the biological technologies of polio vaccine and cytoplasmic sterility. Who could have argued against the benefits of polio vaccine in the 1950's?—yet the vaccine received by millions of people in the United States and abroad is now known to have been contaminated with SV40, a monkey virus which causes tumors in hamsters, though not, as luck would seem to have it, in man. Cytoplasmic sterility is the plant breeder's key to the miraculously high yields of American corn; in 1970, by which time most of the nation's crop was planted to the same successful strain, a blight to which the strain happened to be genetically susceptible wiped out 20 percent of the crop. This is the feeding equivalent, as one speaker pointed out, of 32 billion McDonald's hamburgers.

The conference's first attempt to grapple with its own risk-benefit situation was a document prepared beforehand by a working group under Richard Novick (Public Health Research Institute, New York). The group had looked chiefly at the first of the three types of experiment cited in the original moratorium—the use of plasmids or bacterial viruses as the vector parts of hybrid molecules. It had ranked possible experiments in six classes according to their expected degree of hazard and recommended for each class physical containment procedures which, in the group's judgment, would reduce the biohazard to an "acceptable" level of risk.

The group considered that its work could end up as "the nucleus of a definitive proposal," under which most experiments could be carried out under the appropriate degree of physical containment. The document was attacked by Lederberg for being too precise in its language—legislators would translate it into a "message from on high from which all further exegesis is forbidden"—but the heavier onslaught came from Brenner, who declared that the conference was not going to act as a licensing authority, and that if it did he would resign from the organizing committee. The issue he said,

> is how to proceed in this area without presenting any risk to ourselves, to the innocent within our institutions, or to the innocent outside them. . . . I think there are people here who feel that there will be a negotiable set of compartments and that any particular compartment would comply with their local conditions. I am utterly opposed to that way of thinking. . . . If people think they are going to get a license from this meeting, a notice they can put up on their door, if they are just pretending there is a hazard and are going along with it just so that they can get tenure and be elected to the National Academy and other things that scientists are interested in doing, then the conference will utterly have failed.

The next event was when Watson got up and said he thought the moratorium should end. This was surprising because Watson had been a member of the committee that asked for it. The reason, he explained, was that

> when we met I thought we should have 6 months to see if we could hear anything that would frighten us. As someone in charge of a tumor virus laboratory, I feel we are working with something which is instinctively more dangerous than anything I have heard about here . . . . The dangers involved are probably no greater than working in a hospital. You have to live with the fact that someone may sue you for $1 million if you are careless. That sounds very negative and right-wing but I don't see any other way of doing it."

Watson was speaking for one side of an important divide in contemporary molecular biology, the cancer virologists and old-style microbiologists who are used to dealing with highly infectious agents and to whom, for example, such habits as shutting off washroom faucets with their elbows instead of hands were evidently second nature. Several of them spoke with horror of the "sloppiness" and "prostitution of microbiological technique" of the younger molecular biologists who have recently invaded the field but still treat viruses and bacteria as just another bench reagent. "It is the *E. coli* people who are screaming," said one tumor virologist who, like Watson, believed that the standard precautions were adequate, and that it was really a matter of whether individual scientists took any notice of them or not.

Over the next two days the conference discussed the reports of working parties studying the other two categories of experiment covered by the moratorium. The group under Aaron Shatkin (Roche Institute of Molecular Biology, New Jersey) considered the experiments involving animal viruses as the vector and concluded that they could be safely proceeded with under existing National Cancer Institute (NCI) guidelines for handling oncogenic viruses. One of the group's members disagreed. In a cogent minority view Andrew M. Lewis (National institute of Allergy and Infectious Diseases) argued that no experiments should be undertaken until biologically safe vectors had been developed, and only then under the safety conditions judged suitable by the NCI for medium-risk cancer viruses.

A third working group under Donald Brown (Carnegie Institution of Washington) studied the class of experiments in which genes from animal cells would be inserted into bacteria. (The Berg committee had not embargoed this class but asked only that it be undertaken with caution.) A much discussed example of this class is the so-called "shotgun experiment," in which the total DNA of an organism is chopped into fragments, and the fragments inserted into bacteria and grown up in clones. The most obvious danger is that one of the clones may contain the genes for a hitherto repressed tumor virus. Brown's group ranked experiments in order of hazard, placing the shotgun experiment with primate DNA at the top of the danger scale.

The three working groups were largely composed of the people active

in the field who had been most affected by the moratorium. For many of them, their chief concern was for the conference to agree to or amend the safety guidelines proposed so that they could get back to work again. But attempts to get the guidelines debated in detail were repeatedly sidetracked by people who raised more general issues, and the experimenters were generally unable to refocus the discussion. "The consensus here is that people want guidelines and containment so they can go and do their experiments, but no one will come out and say it—they're all chicken," one group leader observed privately.

The central dilemma the experimenters faced was that, despite the various attempts to rank the experiments in order of risk, no one had any real idea of what the risk might be or how to assess it, a point made in the following exchange on how precisely the guidelines could be written:

MAALOE (University of Copenhagen). I think we are misbehaving ourselves very considerably at this moment because it is nonsense to my mind to try to proofread your report. . . . To imagine that we can lay down even fairly simple general rules would be deceiving ourselves. . . .

LEDERBERG. If it is likely to be crystallized into legislation, we had better be sure that it is right.

BERG. If you concede there is a graded set of risks, that is what you have to respond to.

WATSON. But you can't measure the risk. So they want to put me out of business for something you can't measure.

Photocopying: High Court Tie Vote Leaves Issue to Congress

A long succession of inconclusive answers to the question of whether royalties should be paid when copyrighted material is photocopied was further extended on 25 February when the Supreme Court reported a four to four tie vote on the issue.

The court had agreed to consider an earlier Court of Claims decision, and the effect of the tie was to uphold the lower court ruling allowing the National Library of Medicine (NLM) and the library of the National Institutes of Health (NIH) to go on filling individual requests for copies of single journal articles.

The Court of Claims had acted in a suit brought by the scientific publisher, Williams & Wilkins of Baltimore, charging that NLM and the NIH library had infringed copyright laws by their photocopying practices.

Both sides agree that no sweeping implications can be drawn from the Supreme Court action, since the justices wrote no opinion and because the original case bore on such narrow issues involving particular libraries. (Associate Justice Harry A. Blackmun, who would have cast the decisive vote, disqualified himself in the case. Blackmun did not state his reason for doing so, but legal work he had done for the Mayo Clinic in the past may have been the cause.) There is also general agreement that the matter can be settled more satisfactorily by congressional revision of the copyright law of 1909 than by court action.

The Supreme Court deadlock does not quite close out the available legal options open. Williams & Wilkins could petition the court for a rehearing. But the Baltimore publishers have been receiving help from a sizable group of publishers in paying the substantial legal costs of the Supreme Court test, and the consensus of the group is that it would not be wise to press on. This view, which Williams & Wilkins have accepted, seems to be based on an appraisal of the odds in the court and the feeling that the even split in the court's decision would not count against the publishers when Congress came to consider the issue of photocopying.

Congress Likely to Act

Prospects for this happening soon improved when the Senate last September, after more than a decade of wrestling with the complex issues involved, passed a copyright revision law. The 93rd Congress, however, adjourned without the House's acting on the measure. A virtually identical bill has now been reintroduced in the Senate and is expected to be reported to the Judiciary Committee by the end of April by the subcommittee headed by Senator John L. McClellan (D–Ark.).

In the House, the Senate bill has been introduced by Robert W. Kastenmeier (D–Wis.) and will provide the basis for hearings on copyright revision scheduled to begin in late April before the Judiciary subcommittee Kastenmeier chairs. Capitol Hill observers say chances are good for favorable congressional action on copyright revision legislation by the end of the 2-year life of the present Congress.

A fresh element was introduced into the copyright debate at the end of the last session when an interim copyright bill was passed. This hastily concocted measure did such things as extend certain expiring copyright provisions and increase penalties for counterfeiting sound recordings. But it also called for establishment of a National Commission on New Technological Uses of Copyrighted Works. Among the problems created by new technology which the 13-member commission was directed to study was library photocopying. The commission, which has a $2.5 million budget, is to report within 3 years.

It is conceivable that Congress will choose not to act on library photocopying until the commission makes its recommendations, but it seems likelier that the subject will be covered sooner in legislation. If the treatment of library photocopying follows the line developed during Senate work on the bill (*Science*, 28 June 1974) the practice of libraries copying single articles for those who request them would be sanctioned, but there would be limitations placed on "systematic" copying.

There seems to be a growing conviction among people on both sides of the dispute—authors and publishers and librarians—and among those in the middle—legislators and congressional staff people—that even the most carefully drawn legislation on library photocopying can only provide general guidelines and that agreement on actual practice can best be worked out between the interested parties. While the antagonisms developed have not disappeared, the most serious efforts in recent years involving publishers and librarians to find a modus vivendi are reported to be in progress. There seems to be a realization that even after Congress and the courts have acted the two parties will still have to work it out.—J.W.

SAMBROOK (Cold Spring Harbor). As far as I am concerned there is no absolute containment [for hazardous materials] and all containment is inefficient.

COHEN (Stanford University). If the collected wisdom of this group doesn't result in recommendations, the recommendations may come from other groups less well qualified.

SINSHEIMER (Caltech). Watson says quite correctly that there is no way to measure the risk. But it would seem to me that in the end we will be regulated. We would be in a better position to face that if we take the position that some of the higher [risk] categories of experiment should not be done until more information is available. I can't think of anything that would impede science more than an epidemic around Stanford.

Lawyers Warn of Disaster

The final evening of the conference was surrendered to a panel of lawyers with an interest in the public policy dimensions of science. Perhaps the most telling point was made by Roger Dworkin (Indiana University), who said that any reasonable scheme the conference came up with would be a success but that "any appearance of self serving will sacrifice the reservoir of respect that scientists have and will bring disaster on them." The law has a tradition of letting professional groups regulate themselves, but if they abuse that discretion, as the medical profession has done, they will find themselves being "massacred" in the courts.

Dworkin's point was followed up by Brenner:

> The issue that I believe is central is a political issue. It is this: we live at a time where I think there is a great anti-science attitude developing in society, well developed in some societies, and developing in government, and this is something we have to take into consideration. . . . Who really believes that natural science will increase your GNP? Maybe this is the end of this era. It is very hard to tell in history where you really are. . . . I think people have got to realize there is no easy way out of this situation: we have not only to say we are going to act but we must be seen to be acting.

With such thoughts possibly in mind, the delegates assembled the next morning to learn the organizing committee's opinion of their consensus. The document the committee had finished at about 4:30 a.m. that morning possessed considerably more bite than any of the sets of proposals drawn up by the three working groups. The most innocuous category of experiments were to take place in the "low risk" conditions of physical containment recommended by the NCI for handling tumor viruses such as SV40. All others were to be done in "moderate risk" or "high risk" conditions and were moreover to await the development of biological barriers in the form of bacteria unable to survive outside the laboratory and vectors designed to grow only in certain hosts. (High risk containment, to put these conditions in perspective, involves such measures as showering on leaving the laboratory and negative air pressure, and is generally reserved for handling the most dangerous known human pathogens, such as Lassa fever and plague.) Since many of the safe bacteria and vectors will not be available for months or even longer—Cohen at one point likened their arrival to waiting for the Messiah—the effect of the organizing committee's statement is to continue the moratorium, and in fact to extend it into the class of experiments originally excluded.

Berg presented the statement with the observation that it was the organizing committee's opinion of the consensus of the conference. This was somewhat adventurous in that, as one delegate pointed out, some of the statement's more rigorous prohibitions were being introduced for the first time. The organizing committee's positions were assailed by several members of the working groups who considered them too strict. Stanley Falkow (University of Washington, Seattle) complained that the plasmid group's document had been "prostituted" in the use made of it by the organizing committee. Cohen charged that the "bias of the organizing committee" was reflected in their adoption of the NCI's containment standards for tumor virus research, whereas other government standards relating to bacteria would have been more appropriate.

It was clear that the organizing committee did not intend to have its statement amended from the floor and was even reluctant to test its popularity against a vote. When a voting procedure was forced, the committee turned out to be reflecting a consensus that was every bit as solid as the committee pretended it to be. Its decisions on all three classes of experiment were upheld in separate votes by almost everyone present, with at most five hands raised in opposition. The committee lost on only one point, a motion raised by Robert Williamson (Deatson Hospital, Glasgow) that a class of experiments rated at highest risk by several groups should not be performed under any circumstances, however good the containment. Berg at first resisted the suggestion—presumably because it would have represented a restriction, however formal, on academic freedom to research—but then allowed a vote, which passed with only five people dissenting.

Russians Voice Approval

With the business of the conference essentially complete, a spokesman for the Russian delegates stood up and said the organizing committee's statement was reasonable and acceptable and would be a useful guide for the relevant discussions in the Soviet Union. A final vote was taken to approve the entire statement of the organizing committee, which was approved with only two opposing votes (Cohen and Lederberg). One of the lawyers, Daniel Singer (Hastings Institute of Society, Ethics and Life Sciences), said it had been a moving experience for him as an outsider to watch the group grappling with a very difficult problem. Baltimore then paid tribute to Berg for his pivotal role in the conference's success, and with that the meeting was over.

A press conference held afterward was attended by the major newspapers of the country and *Rolling Stone*. Berg, weary from lack of sleep, was asked if he thought his original call for a moratorium was an overreaction. "Not at all. It has raised the level of discussion about this issue. Six months ago we had daily phone calls asking for pSC101 [a plasmid vector that confers resistance to tetracycline]. I would ask people what they wanted to do with it. Some of them had horror experiments planned with no thought of the consequences. But I was in the same position myself because I was going to do a similar experiment two years ago and someone called me up and asked if I had thought of the consequences."

There is a direct line of descent from Berg's first scruples to the decision reached by the Asilomar conference last month, but the sequence of events was by no means a foregone conclusion. Probably few other people could have asked for a moratorium, got it to stick worldwide, and then handled the issue with the openness and disinterest that disarmed resentment and led the world's scientific community to a notable and generally harmonious consensus.—NICHOLAS WADE