Genetic Manipulation: Temporary Embargo Proposed on Research

Because of a remote but possible hazard to society, a group of molecular biologists sponsored by the National Academy of Sciences (NAS) has called for a temporary ban on certain kinds of experiments that involve the genetic manipulation of living cells and viruses. This is believed to be the first time, at least in the recent history of biology, that scientists have been willing to accept any restrictions on their freedom to research, other than those to do with human experimentation.

The group's proposals, published in this week's editions of *Science* (page 303) and *Nature*, take the form of an appeal to colleagues throughout the world that they follow the group's members in voluntarily deferring for the time being two related types of experiment, and in exercising caution before proceeding with a third.

In addition, the group, known as the Committee on Recombinant DNA Molecules, suggests that the National Institutes of Health (NIH) appoint a committee to give practical guidance on the situation, and that an international meeting of scientists be convened early next year to discuss how to proceed further.

The group is chaired by Paul Berg, chairman of the Stanford University department of biochemistry, and most of its members are scientists who are already active in, or have considered entering, the research field in question.

The primary object of the proposals announced this week is to buy time for further thought before the rapidly developing research field grows too large to be controlled. It is unclear how far and for how long the appeal will be heeded.

Also uncertain is whether the ban will be observed by countries interested in the new technique's considerable potential for biological warfare. Many millions of dollars were invested at the U.S. Army's biological warfare laboratories at Fort Detrick, Maryland, in trying—without much success—to improve on the lethality of viruses and bacteria harmful to man. The new technique offers a theoretically possible way of accomplishing precisely that.

The motivation of the Berg group's proposals springs not from any long-range misgivings about biological warfare or the social impact of genetic engineering, but rather from direct concern about the health hazard presented by the genetically altered bacteria that are created with the new technique. The group recognizes that adherence to its recommendations "will entail postponement or possibly abandonment of certain types of scientifically worthwhile experiments" but says that its concern "for the possible unfortunate consequences of indiscriminate application of these techniques motivates us to urge all scientists working in this area to join us in agreeing not to initiate experiments of Types I and II . . . until attempts have been made to evaluate the hazards . . . ."

The new technique, briefly, depends on the use of a newly discovered class of enzyme to introduce particular genes of other species into living cells such as bacteria. The two types of experiment the Berg group says should be eschewed are those that involve inserting into bacteria (i) bacterial genes which confer either resistance to antibiotics or ability to form bacterial toxins and (ii) the genes of viruses. The potential danger—and it is no more than a theoretical possibility—is that the bacteria endowed with such genes might escape and infect the population, particularly since the standard bacterium used by molecular biologists is *Escherichia coli*, a common inhabitant of the human gut.

A third type of experiment—inserting animal genes into bacteria—is one that the group says "should not be undertaken lightly." This is the recommendation that may cause the most controversy. Some scientists consider the group should have proposed a ban on this type of experiment as well, yet those working in the field consider it the key to significant and immediate discoveries, such as elucidating the structure and working of animal chromosomes.

The Berg group's announcement is apparently the first time that biologists have publicly called attention to the possible public hazards of their own research since November 1969 when a team of Harvard scientists—Jon Beckwith, James Shapiro, and Larry Eron—warned of the dangers of government use of science on the occasion of announcing their isolation of a pure gene from a bacterium.

The Berg group's suggested embargo on gene insertion experiments is also remarkable in that it is the first time—at least within the memory of many people consulted by *Science*—that researchers have ever suggested that their own line of investigation should be halted. Others view the proposed halt less dramatically, as just an extension of the existing restrictions on human experimentation. According to Berg, the embargo is "the first I know of in our field. It is also the first time I know of that anyone has had to stop and think about an experiment in terms of its social impact and potential hazard."

Will the Embargo Stick?

How will the group's recommendations be received by the scientific community? The proposals have been discussed with colleagues and at several scientific meetings with apparently favorable response. "I think the recommendations will stick," says group member David Baltimore of MIT, "because they are reasonable, and the better part of the scientific community recognizes the need for caution. The worse part will be under a kind of moral pressure to go along with the majority." According to Berg, "Anybody who goes ahead willy-nilly will be under tremendous pressure to explain his actions."

Others are less optimistic that those not represented on the group will blindly follow its recommendations. "Caltech and Harvard will respect them, but those not in the elite will see no reason to hold off," says the editor of a biological research journal. "Anyone who wants to will go ahead and do it," is the verdict of an NIH scientist, who adds that although the technique requires a moderate degree of sophistication at present, it will be a "high school project within a few years."

A preliminary tasting of opinion suggests that the majority of scientists will firmly endorse the group's recommendations for a temporary ban on type I and II experiments (introduction

of other bacterial or viral genes into a bacterium). But at least three kinds of objection can be expected from responsible critics.

First, there are those who believe the ban should have been extended to cover type III experiments (introduction of animal genes into bacteria). Virologist Wallace P. Rowe, of the National Institute of Allergy and Infectious Diseases, considers that such experiments should only be done when bacteria are found that are quite unable to infect man. Another NIH scientist, Robert G. Martin, feels the Berg group should have recommended "complete abstinence" from type III experiments. (Martin, who is chairman of the NIH biohazards committee, stresses that this is his personal, not official, opinion.)

A second source of criticism may be scientists who believe that type III experiments present no hazard to health. Donald D. Brown, for example, of the Carnegie Institution of Washington, plans to put into bacteria the set of silk moth genes that govern the synthesis of silk protein.

"I cannot see how this could cause any conceivable danger to anybody," says Brown who, however, supports the embargo on type I and II experiments. The Berg group is concerned about the introduction of animal genes into bacteria because some animal cells possess the genetic instructions for tumor viruses. Brown, however, believes that any putative viruses inserted into bacteria as a by-product of inserting the silk protein genes will not be a serious problem. (To the objection of one scientist that someone infected by a silk gene-containing bacterium might end up with a "gut-full of silk," Brown replies that, because of differences between bacterial and animal cells, the bacterium would probably produce only copies of the silk gene itself, not of the protein the gene specifies.)

Other type III experiments already carried out include the introduction into bacteria of frog genes and genes from the geneticists' workhorse, the *Drosophila* fruitfly. The promise of these experiments, particularly those involving work with *Drosophila*, is so great that those involved in the area are likely to resent any suggestion that the group's admonition of "carefully weighing" their plans be construed to mean they should be stopped or even postponed.

A third kind of objection may come from those who fear that the mere formalization of such proposals will lead to further impediments on research and remove the ultimate decision from the hands of scientists. "The underlying purpose is excellent," says Joshua Lederberg of Stanford University, "but there is already such a momentum toward the regulation of research that the proponents should carefully consider the consequences of stating such recommendations." A quite contrary view is that of Beckwith, who says he is "happy to see this precedent set because it will raise a debate about academic freedom to pursue whatever research one wishes."

At first appearance the Berg group is vulnerable to portrayal as the fox set to guard the chicken coop. The group's unfoxlike recommendations are evidence to the contrary. Moreover, the group's statement, although endorsed by the NAS, is intended to be the personal appeal of the signatories, a fact which may mitigate criticisms that the group has too narrow a membership.

The history of the Berg group's proposals stems directly from Paul Berg's own dilemma as to whether to proceed with an experiment of the type he has now forsworn. Two years ago he managed to synthesize a hybrid DNA molecule which contained a monkey tumor virus named SV-40. Though designed for other purposes, the hybrid molecule would have produced interesting results if introduced into the human bacterium *E. coli*. The problem then arose: what if the *E. coli* containing the monkey tumor virus should escape and infect the population at large?

"I was the first to whom concerns like these were expressed," Berg said last week. "At first it got my back up, but eventually I decided not to do the experiment because I couldn't persuade myself that there was zero risk."

Berg's technique for creating his hybrid molecule was fairly sophisticated but scientists at Stanford and at the University of California, San Francisco, soon developed a simplified adaptation of the technique to introduce frog genes into *E. coli*. "That upped the ante," says Berg, "because it showed how simple it was to introduce any gene you liked into bacteria."

One of Berg's colleagues at Stanford, Stanley N. Cohen, had earlier used the simplified technique to join together two bacterial genes that confer resistance to antibiotics. Cohen described this experiment at a Gordon conference last year. His talk provoked a debate about the implications of hybrid DNA molecules, as a result of which the chairpersons of the session, Maxine Singer of NIH and Dieter Soll of Yale, were instructed to write to the NAS asking that the academy appoint a committee to consider the question. The letter was also published in *Science* (21 September 1973, page 1114).

NAS president Philip Handler directed an academy staff member, Leonard Laster, to follow up on the matter, and Laster asked Singer what the NAS should do. Singer said they should ask Berg ("He was always asking questions about this, and never brushed these questions aside," she told *Science* last week), and Berg replied that he would like to consult others before tendering the academy advice.

With Laster's assent, Berg then got together a group of colleagues who met at MIT this April and agreed that the problems of using the restriction enzyme technique should be put before an international conference, and that the NAS should be so advised.

The conference, however, could not be convened before next February, and meanwhile the new technique was being taken up so rapidly that it seemed many "bad molecules" might have been created before the conference could take action. Berg and his colleagues therefore drafted as a personal appeal the letter that appears on page 303 of this issue. The letter was subsequently accepted by the NAS as representing the committee's report. The NAS endorsement gives the statement an even stronger right to a hearing, though does not in fact mean that the group is claiming to speak for anyone other than themselves.

Prospects for Genetic Engineering

The new technique is a major step toward genetic engineering, since it renders genes accessible and manipulable in a way that has been impossible hitherto. The technique opens up a host of scientifically interesting possibilities. Practical applications remain at the same time very near and very far. One that is often talked of is the possibility of manufacturing insulin by isolating the relevant human gene and adding it to bacteria, which could be cultured and harvested. With use of the restriction enzymes, it looks as if it should be possible to slice up the genetic material of human cells into fragments containing a few genes each, insert the fragments into bacteria, grow thousands of colonies of bacteria,

and select the one which contains the gene for insulin (or more precisely, for the protein from which insulin is derived). But though there may seem to be no theoretical obstacles to such a procedure there are numerous practical problems which are nowhere near solution. For a start, it is not known how well, if at all, the genes of higher cells will be transcribed and translated by bacteria.

The utility of restriction enzymes is that they snip the enormously long DNA molecules of living organisms into manageable fragments which are of roughly the order of a gene in length. (This is because the specific sequence of bases at which each enzyme acts tends on the average to occur this distance apart). A second important feature is that some restriction enzymes, when they cut the double-stranded DNA molecule, slice one strand a few bases lower down than the other, leaving what are known as "sticky ends." Since any species of DNA cut by the same enzyme will have the same kinds of sticky ends, the lower part of one DNA molecule will stick back equally well onto the upper part of another molecule. This is the basic trick whereby two different species of DNA can be annealed into a hybrid molecule.

The way the hybrid is introduced into bacteria is to choose as one of its members—the other is the gene to be inserted—a piece of bacterial DNA known as a plasmid. The plasmid DNA is able to enter the bacterium and get itself (and its hybrid partner) replicated by the bacterium's machinery.

Whatever the prospects for genetic engineering, this is not the reason for the group's suggested embargo. "It is not to be lumped with the proposals saying, 'This is a research path down which we cannot tread because we can't live with the information we will get,'" observes NAS president Handler. The embargo is quite narrowly focused on the specific health hazards potentially raised by genetically altered bacteria, and is framed so as to command the maximum possible agreement among the scientific community. Quite possibly the embargo will be observed until the conference in February. Its real test will come when and if the conference decides the hazard is substantial enough for the embargo to be indefinitely extended. It could then become apparent that control of the new technique is not much easier than the containment of nuclear weapons.

—NICHOLAS WADE

Advising the White House: NSF Says the New System Works

H. Guyford Stever, who is the President's science adviser as well as director of the National Science Foundation, says that he sees President Nixon only on formal occasions and never engages him in "intellectual Ping-Pong games" over policy matters. But Stever regards this relationship as a reflection of Nixon's personal style of management and of the changing character of science-related issues, and not as an indication of a White House animus toward science.

Moreover, Stever contends that the NSF's two, semi-autonomous advisory units—the Office of Energy Policy and the Science and Technology Policy Office—have begun to establish close working relationships with key decision-makers in the Executive Office. And he says that in some areas the OEP and STPO have begun supplying the White House policy machinery with analytical reports and advice on a larger scale than did the old White House Office of Science and Technology.

This was the thrust of a recent interview with Stever and three of his top aides, following the National Academy of Sciences' release of a report criticizing the new science advisory apparatus Stever directs. The report, written by a special panel headed by James R. Killian, Jr., exempted Stever and his staff from criticism but concluded that the "two-hat" system under which he now operates is inherently unworkable. The Killian panel called instead for the creation of a new Council on Science and Technology in the President's Executive Office (*Science*, 5 July).

H. Guyford Stever

On 10 July, former science advisers to Presidents Eisenhower, Kennedy, Johnson, and Nixon joined the chorus of elders calling for a restoration of science advice in the White House. Seated together in the hearing room of the House Committee on Science and Astronautics, George Kistiakowsky, Jerome Wiesner, Donald Hornig, and Lee A. DuBridge echoed the Killian panel in contending that the NSF is too far from the center of action to effectively advise the presidential policy machinery. And they said the NSF lacks the bureaucratic clout to maintain discipline among the federal agencies.

Like the Killian panelists, the former science advisers pointedly refrained from criticizing Stever and his staff, and applied their reservations instead to the role in which the NSF has been cast since the demise of the OST. "The two-hat system is impractical," Wiesner noted. "When I was science adviser it was a 24-hour-a-day job and I wasn't trying to run an agency on the side." Kistiakowsky predicted that as "mistakes are made and irritations occur, Stever will become even less effective."

If the House science committee sticks to its present plan, Stever's side of the science policy debate won't be heard officially until the hearings are con-