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NEWS AND COMMENT

Recombinant DNA: The Last Look Before the Leap

The tortuous and possibly historic debate on whether to proceed with research on recombinant DNA is now nearing the end of its first round, with a clear victory in sight for those who wish research to go ahead under stiff but not grossly inconvenient safety conditions.

This is the course that is favored by probably a vast majority of biological researchers. Yet it is worth noting the strong dissent of two scientists who are as eminent as any of the contributors to the debate, and who in addition have no personal interest in using the technique. Robert Sinsheimer, chairman of the biology division at Caltech, believes that all research should be confined to one site, such as the former biological warfare laboratories at Fort Detrick. Erwin Chargaff of Columbia University would like to see the research prohibited altogether to allow a two-year period of "cooling off" and reflection.

These views occur in written comments solicited by National Institutes of Health director Donald S. Fredrickson. On the basis of the comments, and of the record of a public hearing on the issue (*Science*, 27 February 1976), Fredrickson has proposed some minor emendations to the present draft guidelines on recombinant DNA research prepared by an NIH committee. At a two-day meeting held on the NIH campus last week, the same committee considered and rejected most of them.

Whether or not Fredrickson accepts the committee's advice, the guidelines that he will issue within the next few weeks will not differ greatly from the present draft.

It is perhaps a pity that Sinsheimer's views were not discussed by the NIH committee last week because, though not widely held, they are by no means negligible. Moreover, Sinsheimer seems to have a broader sense of perspective than others about the place of the new technique both in history and in evolution. His critique of the guidelines is premised on a fundamental and so far unrefuted theorem, that there is a barrier to genetic exchange between the two great classes of living things, the prokaryotes and the eukaryotes. (Prokaryotes are primitive cells, such as bacteria and blue-green algae, which lack a nuclear membrane; eukaryotes, the cells of all higher organisms, have a quite different and more sophisticated organization.)

Many of the proposed experiments with recombinant DNA involve inserting segments of eukaryotic DNA into prokaryotic cells, and the whole thrust of the guidelines has been to rank these experiments in a graded series of risks based on the nature of the eukaryotic DNA segment. Sinsheimer, however, believes that the risk lies not in the particular DNA being inserted, but in the very fact of putting eukaryotic genes into prokaryotes. If he is right, the elaborate edifice of rules constructed by the NIH committee is built on a foundation of sand.

Sinsheimer's argument, as expressed in two letters sent to Fredrickson in February, goes as follows.

Though prokaryotes and eukaryotes interact intensely with each other as organisms, they are not known to interact with any frequency at the genetic level. One evident reason for this lack of genetic intercourse is that, though they use the same genetic code, they have different control elements, different genetic signals for governing how the code is to be put into operation. The great danger of putting any piece of eukaryotic DNA into a prokaryote is that it may endow prokaryotes with the eukaryote control signals, a sort of betrayal of state secrets at the molecular level. Even if this occasionally happens by accident in nature, Sinsheimer says, numerous experiments of the type envisaged can only increase the risk.

What might be the consequences of breaching the natural barrier between prokaryotes and eukaryotes? One is that the prokaryotic viruses, particularly the lysogenic species, could acquire the capacity to infect eukaryotes. A bacterial virus carrying the gene for a restriction enzyme, for example, could wreak havoc inside a eukaryotic cell. Another pos-

sibility is that bacteria might acquire the capacity to serve as reservoirs for some of the common eukaryotic viruses. "One need not continue to spin out potential horror stories," Sinsheimer says. "The point is that we will be perturbing, in a major way, an extremely intricate ecological interaction which we understand only dimly."

Because of these risks, Sinsheimer would like to see all recombinant DNA work performed at one site in the country, such as Fort Detrick. Meanwhile a major program should be launched to find a more suitable host for recombinant DNA molecules than *Escherichia coli*, the present candidate of choice. With recombinant DNA experiments being performed in hundreds of laboratories about the United States, organisms "will inevitably escape—and enter into the various ecological niches inhabited by *E. coli*." It would be better to employ as host a bacterium that only grows in special environments (such as the thermophiles that live in hot springs), or else to incorporate DNA into an animal virus, such as cowpox, against which we already have a viable defense in the form of vaccination.

"Obviously," Sinsheimer concludes, "neither I nor anyone else can say that if the present committee guidelines are adopted, disaster will ensue. I will say, though, that in my judgment, if the guidelines are adopted and nothing untoward happens, we will owe this success far more to good fortune than to human wisdom."

Sinsheimer's barrier theorem arouses strong disagreement in many other biologists, though the strength of the reaction generally relates to fear that his views will be used to impede research rather than to any obvious flaw in the argument. Those who disagree point out that the barrier to genetic exchange may only seem to exist because of our ignorance about the flow of genes between species. For example, it now seems possible that viruses may play an important evolutionary role by transferring genes between species and allowing one species to sample the genetic progress being made by others. Nevertheless, such mechanisms are not yet known to operate across the presumptive prokaryote-eukaryote barrier.

Another argument raised against Sinsheimer's hypothesis is that the barrier, if it indeed exists, may have come into being as the accidental by-product of some other process and have no inherent purpose in itself. In other words it is contingent, not a specific mechanism designed for evolutionary reasons to keep eukaryotes and prokaryotes in genetic apartheid.

Nevertheless, Sinsheimer's theorem does not appear at present to be literally refutable, even though many disagree with it. "It's evolutionary speculation. I don't believe it for a minute," says David Botstein of MIT. If Sinsheimer cannot be directly refuted, probably the best of the indirect arguments raised against his position is the view that further experiments will answer the questions he raises. "What will deal with Sinsheimer is experiments, on the basis of which we will know what to be careful about," says Botstein. For similar reasons, Matthew Meselson of Harvard says that the work itself will reduce the hazards.

Another strongly held belief of those who oppose Sinsheimer's position is that recombinant DNA research is urgently required as insurance against forthcoming catastrophes. David Hogness of Stanford, for example, points to the need to feed increasing populations. Meselson sees the technique as the key to reducing man's total vulnerability to viruses. "Most species that have ever existed are gone now, and they seem to vanish randomly in time," says Meselson. "We don't know why, but there is nothing like a virus infection to give that kind of statistics. You could argue that knowing how viruses spread, which this research will tell us, should be of the highest priority."

This is not a trivial consideration, but neither is Sinsheimer's view that scientists simply may not have the right to create novel organisms likely to spread about the planet in an uncontrollable manner for better or worse. There has been no explicit consideration, he said in a recent lecture to the Genetics Society of America, "of the potential broader social or ethical implications of initiating this line of research—of its role, as a possible prelude to longer-range, broader-scale genetic engineering of the fauna and flora of the planet, including, ultimately, man. . . . Do we want to assume the basic responsibility for life on this planet—to develop new living forms for our own purpose? Shall we take into our hands our own future evolution?"

At its meeting last week the NIH Recombinant DNA Molecule Program Advisory Committee addressed itself not to these questions but, at Fredrickson's behest, to changing jobs and tittles in its draft. Fredrickson's position, which in effect is to endorse the present guidelines, may indeed be merited, but it also happens to fall within the limits of two quite cogent political constraints. The first is the attitude taken by European countries toward the present guidelines. In a maneuver of some finesse, the European Molecular Biology Organization (EMBO) won itself almost a veto power over Fredrickson's decision by making known that it would only go along with the NIH guidelines if they became no stricter. Thus if European-American unity were to be preserved, a generally desirable objective, Fredrickson could make few substantive changes in the guidelines. As he observed at last week's meeting, "Without a certain measure of conformity, the whole exercise would be futile."

A second constraint is the possibility of the guidelines being ignored altogether if made unacceptably rigorous. Were the Sinsheimer suggestion to be adopted, says an NIH staff member who helped analyze the public's comments for Fredrickson's decision, "the research would go on under other conditions anyway, so that wouldn't be an effective stance for NIH to take even if we agreed with it."

[Most of Fredrickson's proposed emendations to the guidelines concern raising the safety levels required for particular kinds of experiments. (The safety levels are designated, in increasing severity, P1 to P4 for physical methods of containment, and EK1 to EK3 for biological methods.) His strongest suggestion, unless there "are compelling arguments to the contrary," is to raise the so-called shotgun experiment with the genomes of cold-blooded vertebrates to the level of P3 + EK2. The committee voted to keep it at P2 + EK2. Fredrickson also suggested raising the level of the shotgun experiment with other cold-blooded animals (including insects) to P2 + EK2. In a carefully worded paragraph, the committee essentially agreed to this if the species carries a known toxin, but said that laboratory grown animals such as *Drosophila* should stay at P2 + EK1. (Higher plants, by contrast, whose genomes are not obviously more threatening than those of insects, stay at P2 + EK2). Fredrickson was also turned down on a suggestion to raise work with the SV40 virus from P3 to P4 conditions.]

Since the NIH committee has passed final word on its guidelines, now may be as good a time as any to comment on the balance of forces within it. The two most dominant members have in general been David Hogness of Stanford University and Charles Thomas of Harvard, both of whom have forcefully argued the case against stricter levels of containment. Both, as it happens, are personally interested in doing recombinant DNA experiments, a circumstance which has led to suggestions of a conflict of interest. However that may be, they represent a legitimate and widely held point of view that they would doubtless have argued anyway.

Hogness and Thomas have in fact put their case so effectively that other members felt the issue was being railroaded. Several even turned for help to a group of young Cambridge scientists who, calling themselves the Boston Area Recombinant DNA Group,* produced a cogent position paper in favor of tighter guidelines. It has in fact been largely in response to outside pressures, such as that exerted by the Boston Area Recombinant Group and others, that the guidelines have been increased in stringency.

The NIH committee's hardest working member has undoubtedly been Roy Curtiss of the University of Alabama. He and 8 colleagues have worked overtime for about a year to develop the enfeebled strain of *Escherichia coli* which the guidelines require to be used for many categories of recombinant DNA experiments. Since safety measures for some reason lack glamor, Curtiss and his team may not get the credit they deserve, but it is only through his voluntary efforts that the bacterium will be available just when it is needed. (The committee approved for use an enfeebled bacterial virus developed by Philip Leder and others at NIH. It is expected to certify Curtiss's *E. coli* imminently).

The NIH committee has clearly succeeded in producing a reasonable and scientifically acceptable set of guidelines that will probably be adopted or closely copied throughout the world. Yet Sinsheimer's arguments have raised awkward questions which nobody yet seems able to directly answer. So the present plan is to go ahead anyway and let them be answered by events. That is maybe what has to be done, but it would look better if Sinsheimer's Cassandra-like fears could be proved imaginary first.—NICHOLAS WADE

*The group consists of Richard Goldstein, Paul Primakoff, Margaret Duncan, and Hiroshi Inouye, all of the Harvard Medical School, and Cristian Orrego of Brandeis University. The group is not affiliated with Science for the People, as was erroneously stated in *Science* (27 February).

Biomedical Panel: Urging a Move to Bring Cancer Back into the NIH Fold

It has been 5 years since the passage of the National Cancer Act that elevated the National Cancer Institute (NCI) to privileged status within the National Institutes of Health (NIH). Under that 1971 act, skillfully maneuvered through Congress by forceful cancer lobbyists, the NCI was given two things that suddenly set it above the rest of NIH—truly vast sums of money and direct access to the White House through the creation of a three-member President's Cancer Panel, headed by New York financier Benno C. Schmidt. The rest of the biomedical community has been jealous and out of sorts ever since.

Now, the President's Biomedical Research Panel, established in 1974 to conduct an 18-month study of the country's biomedical enterprise as a whole, is taking what it sees as a first, gingerly step toward restoring the balance. When its report is released on 30 April, it will contain a recommendation that the existing cancer panel assume a dual role. In addition to serving as the senior policy-making body of the cancer institute, it will be asked to oversee policy-making for the rest of biomedical research as well.

On the face of it, it is a contradictory and, frankly, audacious recommendation. Were the President to accept it, the present cancer panel, already the object of distrust, would have its powers extensively broadened almost overnight. Benno Schmidt, the czar of cancer, would become the czar of all of biomedical research, at least until his term on the cancer panel expires 2 years from now.

The about-to-go-out-of-business biomedical panel that is making this recommendation is headed by Franklin Murphy, an M.D. who is now head of the Times Mirror Corporation in Los Angeles. Schmidt is the only layman on this panel. Its other members* are basic researchers and physicians from the nation's most prestigious medical schools. Why, one cannot help but ask, would they make such a recommendation? The answer, as expressed by members and panel staffers, is that they have come up with a clever scheme for eventually getting the cancer institute back into NIH. One said it is a way to "set the stage" for the eventual return of the NCI to fiscal control by NIH. Another described it as a move to "make rational, step-by-step," the present system that allows NCI to go its own way. Underlying it all is the probably correct assumption that if NCI is going to be divested of any of its privileges, this will have to be done with great diplomacy.

The biomedical panel acknowledges the tremendously powerful lobby that backs the present cancer program and concedes that, if it fought the program openly, it would probably lose. It also recognizes that Schmidt, as a member of the cancer panel, cannot, as a member of the current biomedical research panel, be put in the position of having to offend part of his constituency. So, one can suppose, there is a certain logic in giving him responsibility for both. In spite of Schmidt's obvious devotion to the cancer program, to which he gives a good deal of his time, it is true that he has consistently expressed an interest in other areas of research, taking the position that it is neither scientifically nor politically sensible for the cancer community to alienate colleagues in other fields. Furthermore, he has taken a strong, if not entirely successful, stand on the issue of training grants, a provision that is dear to the hearts of investigators in every discipline.

Nevertheless, the thought of having Schmidt, R. Lee Clark, head of the M.D. Anderson Hospital and Tumor Institute in Houston, and one yet-to-be-named new member of the cancer panel assume responsibility for all of biomedical research offends some individuals. The matter came up, for example, at a recent meeting of the National Heart and Lung Advisory Council. In a letter to biomedical panel chairman Murphy, heart council members said they wholeheartedly concur with the establishment of an advisory committee "at the highest level which will have a broad overview of the entire biomedical research enterprise," but they think it should be established "de novo," which is to say, they do not want it to fall into the control of individuals whose first loyalty is to cancer.

All of this raises a little-discussed question about the need for special panels in the first place. The immediate precedent

*Franklin D. Murphy, Times Mirror Corporation; Ewald W. Busse, Duke University Medical Center; Robert H. Ebert, Harvard Medical School; Albert L. Lehninger, The Johns Hopkins University School of Medicine; Paul A. Marks, Columbia University; Benno C. Schmidt, J. H. Whitney and Company, New York; David B. Skinner, University of Chicago Hospitals and Clinics.