



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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BETHESDA, MARYLAND 20014

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Dr. Paul Berg
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Dear Paul:

After carefully considering the events at the recent Tumor Virus Symposium at Cold Spring Harbor, I feel compelled to express my opinion concerning the discussions related to the ligation of heterologous DNA to E. coli plasmids.

In a brief session David Baltimore described the procedure used to make the plasmid-Xenopus mitochondrial DNA recombinant, stressed the simplicity, applicability and the concomitant hazards associated with this technology, and read the statement submitted by the committee established by the National Academy to consider such problems. I came away from this session with the belief that this ligation technique was to be put aside pending further evaluation. Several hours later I was told by one of the members of the NAS committee that my impression was wrong and that (due to the utmost importance of information to be obtained) the utilization of this procedure to explore the genetics of eukaryotic cells would progress unimpeded. Having been informed that the union of DNA to E. coli plasmids could easily become a "high school biology project" I was very disturbed by this revelation. During the remainder of the conference I discussed various aspects of this problem with a number of individuals. These encounters indicated the validity of my original belief and heightened my concern that the NAS committee statement was a guise. Recalling Baltimore's concern about the presence of news media representatives at the biohazard discussion and his emphasis about the need for a carefully contrived press conference to present only the more positive aspects of this development, reenforce this accusation.

Since there is little time before Cohen's manuscript is to appear in PNAS I felt the best approach would be to document my concern by mail.

As a collaborator in the Jackson-Berg technique to ligate units of DNA with the self-replicating λ d v gal plasmid, you are aware of the views of many scientists concerning the potential public health hazards associated with self-replicating recombinants capable of growth in E. coli. It is my understanding that the concern expressed by other investigators caused a moratorium on certain experiments with the λ d v gal-SV40 recombinant i.e., the infection of E. coli with this material. The fundamental basis for the criticism of these experiments was the implication that any technology involving the use of recombinants between plasmids capable of reproducing in organisms which compose human flora constituted an undue public health risk whose consequences were unpredictable.

The Jackson-Berg ligation procedure involved sophisticated biochemistry; thus, it was less likely that this technology would be used or abused by anyone but highly skilled, responsible investigators. Rather than postpone improvements on this procedure and attempt to assess its inherent risks, another procedure has been devised which due to its simplicity raises not just questions of propriety and risks but a spectre which causes immediate concern among all who appreciate such problems. One must question whether or not this improvement in methodology, which was developed at this juncture in spite of widespread criticism of the entire concept, represents an irresponsible act.

It has been argued that once a concept has been formed that it is impossible to retard its development. I disagree. The degree of sophistication now attained by molecular biology and biomedical research makes it imperative that the use and development of potentially hazardous agents and techniques proceed only after careful assessment of the risks involved. Given the furor which has developed over the use of human embryos and embryonic materials, problems related to abortion and testing for sickle cell anemia or trait, it is apparent that public support of the application of certain technologies is uncertain. I should emphasize that these outbursts have evolved from procedures which involve comparatively few individuals. Once there is general public awareness of a technique which can be readily adapted by almost anyone in a "high school biology course" to yield untold numbers of new infectious agents which are potentially capable of spreading throughout the population, the reaction seems to me to be very predictable and its implications far reaching for biomedical research.

In this regard I am compelled to plea for voluntary restraint by the investigators who have perfected this new procedure. To emphasize the need for restraint and to firmly and unassailably establish the genuine concern of these investigators who have already published several articles describing various aspects of this technique, I suggest that Cohen's manuscript and the misleading statement to be issued by the NAS committee which serve to proclaim this dubious achievement be withdrawn. I further suggest that you and the other members of the committee use your considerable influence to see that all work involving the use of plasmids or recombinants capable of replicating in organisms which colonize humans be stopped until a more broadly based group composed of individuals (with other than a vested interest in seeing such work progress) can consider the attendant risks and make totally unbiased judgements as to the constraints necessary before additional work in this area progresses. Unless the investigators involved exert the self-restraint required to lead the scientific community to self-control of such research; the most certain alternative is legislative action at the federal, state, and local level to establish firm control over all public and private laboratories capable of supplying reagents for or carrying on such research.

My position in such matters is based upon my firm conviction that protection of the public takes precedent over self-interest and pursuit of knowledge in situations which threaten the general population with infection by laboratory created agents of unknown pathogenicity. As you know, I have attempted to follow this approach in dealing with the problems associated with release of the nondefective Ad2-SV40 hybrids. It is interesting to note that, due to their concern about restrictions on scientific inquiry, several members of the NAS committee have thus far failed to support the essentially voluntary attempts developed by NIAID to restrict the use of the nondefective hybrids to responsible laboratories. By failing to support and contribute to attempts to control such problems within the scientific community these individuals are ensuring the very regulations which they seem to oppose.

Sincerely yours,



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