

HOW SHOULD RECOMBINANT DNA

RESEARCH BE CONTROLLED ?

An essay based on remarks presented at a hearing before
the Attorney General of the State of New York, October 21, 1976.

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I am a cell biologist, engaged in what I hope is productive cancer research. I hold a Ph.D. in Biology, and I am an Associate Professor of microbiology at Stony Brook. I am a member of the Human Cell Study Section of the National Science Foundation, and an associate editor of the Journal of Virology. I have received most of my training, and done most of my work, in New York State; at Stony Brook, Cold Spring Harbor, New York University Medical School and Columbia University. There I received a B.A. in Physics. I left physics for the freer inquiry of biology, and I am not prepared to lightly give it up.

I have done no work on recombinant DNA, nor do I plan any. I hold no vested interest in the work, and no patents. In 1972, while at Cold Spring Harbor, I was asked by Paul Berg, David Baltimore and James Watson to help organize a meeting at Asilomar, California, to discuss possible hazards of some new techniques, including restriction-enzyme ligation and plasmid amplification of specific DNA sequences. The proceedings of this meeting were published in Cold Spring Harbor as "Biohazards in Biological Research", which I helped coedit.

They asked me to do this in response to my personal apprehension, raised in the Summer of 1971, that unrestricted research on recombinant DNA might be dangerous. Rather than argue over the phone, we agreed that it was necessary to meet, to get these fears out in the open. The moratorium, and the National Institute of Health guidelines followed in time. After all that has happened, I welcome the opportunity to give my own opinion about the current situation.

Recombinant DNA research is worth doing. Our current lack of knowledge about fundamental life processes is indisputable. This ignorance centers about our inability to study the way in which genes are activated, and inactivated, as part of the normal processes of embryonic development and normal differentiation. Gene amplification has no substitute as a probe for understanding these processes. The underlying reason for this is the striking fact that the vast majority of the DNA of any higher organism is silent and unexpressed, and therefore unavailable for classic experimental genetic manipulation. To understand the regulation of gene expression, we require a knowledge not only of the DNA of the genes themselves, but also of the DNA between the genes. These sequences of DNA code not for products which we can assay biochemically, but for "addresses", information needed for regulation. While we cannot study this regulatory DNA by classical genetic techniques, we can clone it out directly through recombinant DNA--plasmid amplification. We will remain ignorant of the mechanism of action of certain diseases so long as we remain ignorant of the mechanism of regulation of gene expression.

To give just two examples of our current ignorance, consider that we have to rely upon injection into a person of vaccines, in order to stimulate the immune response against the disease-causing agent. We do this because we have absolutely no idea how to directly stimulate the gene or genes coding for the immunoglobulin molecules that could directly interact with the offending agent. And we are ignorant of gene control processes in higher organisms in general. Second, both a tumor and a normal tissue share their common origin from a single fertilized egg cell, so it must be a failure in the normal regulation of gene expression, no matter what the initial cause, virus or chemical which yields the tumor. This approach to cancer research depends critically upon being able to analyze the regulation of gene expression in mammalian cells.

Indeed I cannot think of a biomedical problem for which information would not be forthcoming from the technology of gene amplification, especially DNA amplification of inter-gene sequences.

The National Institutes of Health guidelines for recombinant DNA research are workable, with the cooperation and with the education of persons responsible for the research. Education and cooperation do not come without effort. The effort necessary includes a commitment to open our discussions about proposed work to the general public, and a commitment to take seriously the restrictions on free inquiry imposed by the guidelines.

Opinion among scientists as to the effectiveness of the guidelines is divided. I believe that work within the guidelines will be safe. That is, when one works with sufficient physical isolation, and when one's plasmids are in an E. coli of sufficiently suicidal genetic makeup, then one can reduce the probability of recombinant DNA molecules entering the environment to as low a probability as one wants. Indeed I think that the guidelines have been designed precisely to take into account the absence of an assay for the risk at hand, in their dependence upon physical isolation and upon the fastidious, suicidal nature of the organism carrying the recombinant plasmid. Opinions of my colleagues range from an insistence that there is no need for any guidelines, to insistence that no work on recombinant DNA should be done.

I am aware of a concern that scientists, as people, must be self-serving and must be expected to argue only for guidelines that are in their own selfish interests. I cannot see how that is the case, given the intense disagreement within the scientific community. While I am somewhat disturbed by the intensity of these arguments, I am convinced that they indicate at least that scientists are behaving in a democratic way as responsible citizens, in this case. Currently the guidelines are advisory, and therefore it is up to each scientist who chooses to abide by them, to convince those scientists who don't that they must, and to convince those who are against all work to permit work to be done within the guidelines. This constant need to convince is a great strain on all concerned.

Because I believe the guidelines to be adequate, and because I do not wish to see the period of self-enforcement prolonged, I have come to the conclusion that the guidelines should have the force of law, with the New York State requirements for the handling of radioactive material as a model. The guidelines are workable and effective but also, they are necessary to relieve practicing scientists of the constant need to pass quasi-legal judgement on each other, a process I find to be inherently painful, non-scientific and certainly more destructive to free inquiry than the guidelines themselves.

The radioactive materials law is based on the geiger counter which detects radioactive spills. In lieu of any counter to assay biological hazard, the guidelines have provided assays of physical and biological containment. Therefore they operate under the tacit assumption that the risk, which is unknown, is likely to be proportional to dose. This seems sensible to me. However, making the assumption that risk is proportional to dose implies that a big dose of any novel organism is intrinsically more dangerous than a little one. As such, facilities that generate big doses, that is, large volumes of bacteria which carry recombinant plasmids, are the facilities most likely to provide a risk to the public. Since such large facilities are likely to be industrial and since they are not likely to be supported by Federal or State grants, any proposed law should apply across-the-board to all facilities, independent of their support and independent of their purposes.