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Deputy Director for Science
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Bethesda, Maryland 20014

Dear Hans,

I thought it might be useful if I amplified some of the comments I made when we discussed the possibility of federal legislation to regulate research on recombinant DNAs at the last meeting of our committee. I should emphasize at the beginning that I refer specifically to research activities and not to the commercial distribution of some product of that research, which I think could be covered by existing regulatory law.

There is no question in my mind that legislation leading the direct regulation of this research would be a major mistake. We must keep reminding ourselves and others that no one has demonstrated, on the basis of fact, that any hazard is indeed posed by this research. In fact, the information that has been gathered since the inception of recombinant DNA technology leads to the opposite conclusion. It may be worthwhile to summarize some of this information here.

(1) A great variety of recombinant DNAs have been made in a large number of laboratories during the past three and one-half years without causing harm. In my laboratory alone, we have created tens of thousands of different DNA recombinants in which small segments of animal DNAs (in this case, from *Drosophila melanogaster*, the classical organism used over the past 70 years for genetic studies) have been inserted into the bacterium, *E.coli* K12. Equally large collections of recombinants of *D. melanogaster* have been made in several other laboratories, both in this country and in Europe. Similarly large collections of recombinants carrying DNA segments from many other eukaryotes (e.g., yeast, other fungi, silk moths, plants) have been made in other laboratories. In no case has any illness resulting from the handling of these recombinant DNAs been observed. The point is that this area of research is not the infant it once was, and that we are building a considerable base of practical experience that argues against the hazards that some imagine might occur by chance from such

random DNA recombinants.

(2) Experiments carried out both in the U.S. (Dr. S. Falkow, University of Washington, Seattle) and in England (Dr. H. Williams Smith, Houghton Research Station, Huntingdon) demonstrate that the host bacterium, E.coli K12, does not become pathogenic even after the introduction of a plasmid containing a gene that produces a known toxin (the Ent toxin). This plasmid occurs in nature and the gene for the Ent toxin that it carries is known to be active in the E.coli K12 host; yet these bacteria did not become pathogenic, as demonstrated by feeding them to experimental animals. The point made here is clear: if a toxin gene that is designed to be expressed in E.coli K12 does not render this bacterium pathogenic, what chance does a foreign gene, which is not so designed, have? I should emphasize that the plasmid-E.coli K12 system used here was of the garden-variety type, not the highly disarmed systems known as EK2 in the NIH guidelines.

(3) Experiments carried out by Dr. R.W. Davis (Stanford University) demonstrate that vectors carrying segments of foreign DNA are lost when grown in competition with the parent vector, which does not contain the foreign DNA. In these experiments, random segments of yeast DNA were individually inserted into the λ phage vector and a population of the resulting recombinant DNAs collected which contained many thousands of different yeast DNA segments - more than enough to include all of the genes in yeast. To this population was added a very small amount of the parental λ phage vector, such that its concentration in the population was no greater than that for any one of the hybrid DNAs. When this mixture was then allowed to grow, the parental λ phage always displaced the phage carrying the yeast DNA from the population; i.e., the recombinant DNAs could not survive in competition with the parental DNA. The point here is that the synthesis of a recombinant DNA in the laboratory does not necessarily represent an "irreversible" event, as some have argued. This evidence clearly argues against scenarios that involve epidemic catastrophies resulting from recombinant DNAs. Another point should be emphasized that is all too often forgotten - namely that the various niches in this world are already occupied by organisms that are there because they have a competitive advantage over other organisms that may enter the niche. And this advantage generally results from multiple gene differences - not the kind of gene combinations that one could create in the laboratory by random insertion of a small segment of DNA.

(4) Evidence has been obtained demonstrating that genetic exchange does occur in nature between such diverse organisms as bacteria and plants. Thus Dr. Eugene Nester's group at the University of Washington [Nester et al. (1976). 10th Miles Symposium, in press] has obtained direct evidence that genes

from a bacterial plasmid are incorporated into plant cells in nature. While the frequency of such genetic exchanges between diverse species has not yet been determined it would be arrogant of us to assume that what we can do so easily in the laboratory does not occur commonly in nature. When one takes into account the enormous tonnage of flora and fauna that are annually degraded in this world by bacteria, and that the enzymes required for making recombinant DNAs are prevalent in these bacteria, as are the required DNA vectors, then one must infer that the insertion of eukaryotic DNA into these vectors and the subsequent infection of the bacteria by the resulting hybrid DNAs is an every day occurrence. Or put another way, one would have to invent ad hoc inhibitory mechanisms to suppose that it does not occur on a regular basis. The reason that we are only now obtaining evidence for such genetic exchanges is that they have not been looked for previously. And this is because it is only recently that we have understood some of the mechanisms by which such events can occur. [An excellent discussion of the evolutionary implications of such exchanges is given by Darryl C. Reanney (1976). Bact. Rev. 40, 552-590].

I should also like to call attention to the fact that plant geneticists have for some time been mixing chromosome sets from different species with beneficial, not hazardous effects. Here the amount of genetic mixing is much greater than the small amount that can be effected by introducing a short segment of DNA into an extrachromosomal vector such as a plasmid or a virus.

I have taken the time to make this summary because the points it contains are generally ignored by those who would induce fear by creating imagined scenarios of catastrophes that are increasingly divorced from reality. For the Congress of the United States to generate laws regulating recombinant DNA research in the absence of a demonstrated need and based on these fears would indeed be a grievous mistake. For, without factual cause and induced by panic of error, a costly bureaucracy would thereby be created whose sole known effect would be to inhibit the considerable benefits to both health and agriculture that will result from this research. Some of these benefits we can now specify without recourse to speculation. For example, we now know and can define the steps required to produce a medically useful protein, such as insulin, in large amounts in E.coli K12. [I choose insulin for this example because there is a verified and increasing shortage of this protein that cannot be met by existing modes of production]. The number of steps and their precise nature is such that while the end result can be achieved by a series of carefully designed experiments, the probability of producing that result by chance recombinants is so low that it can be ignored.

The reason we can define these steps is that we know so much about gene expression in E.coli K12. To reap other kinds of benefits, such as an increased and cheaper food supply by modification of crop plants, we shall need a comparable knowledge about gene expression in higher organisms. The only way I know of to obtain this knowledge is through the use of the recombinant DNA technology.

All of this research, both the immediately practical and that necessary for the longer range benefits, would be severely inhibited by direct federal regulation. Consider the task of such a regulatory agency. It would have to devise rules that would cover recombinant DNA research with any of all life forms that inhabit this earth, and, being regulatory, would have to determine that these rules are being followed. The only conceivable way it could generate such rules would be to establish a relatively small number of biological boundary lines for classifying this vast area of experimentation. This necessarily means that particular experiments would either not be covered by its rules or would be misplaced within them. Hence it would be plagued with numerous legitimate requests for variances. And remember, we are not talking about the commercial distribution of a limited number of the products of this research; rather we are talking about each and every experiment. The bureaucratic structure required to carry out such a regulatory function efficiently and fairly would be enormous and costly; indeed I doubt if it could be done efficiently. Furthermore such a regulatory agency would have to establish its rules in the absence of any demonstrated hazard, and it is inconceivable to me that many of these rules would not be subject to legal challenge. Finally we know that the data base for these rules will be changing very rapidly (e.g., the data base for the NIH guidelines has already changed significantly since they were issued last June). This means that the rules would have to be continually revised. I submit that the result of a regulatory attempt on this scale would be a nightmare of waste, frustration and inhibition of the talents of this nation.

I suggest the following alternative, which is based on the modes by which bacteria and viruses that are known to be pathogenic to man have been handled safely in hospitals and laboratories throughout this country for decades. No federal regulatory agency overlooks these activities because experience has shown that none is necessary. Rather a standard set of good practices has been taught and followed by these institutions, on the basis of sanity and public conscience. For recombinant DNA research, I suggest that the same mode should be followed, with the difference that the NIH guidelines would define the standards of good practice. They provide an extremely conservative guide for the containment conditions to be used for general classes of experiments. They were formulated after extensive

deliberation in open meetings that invited, received and incorporated much public input. Thus, these conditions of formulation comprised that blend of expertise and public concern which one desires in defining standard good practices. Furthermore, there is no reason why this same responsible mechanism cannot be used to efficiently change the guidelines, and hence the definition of good practice, as the data base changes. The regulatory mode is avoided by this mechanism, and, on the basis of experience with real pathogens, it is legitimate to do so. Certainly a strong element of the absurd would be introduced if the government established a vast regulatory network to oversee experimentation in an area where no hazard has been demonstrated, yet has found it unecessary to do so with known human pathogenic agents.

These comments are more extended than I had originally intended, although I realize that even with this length they do not cover all the bases. I hope in any case that they are of some use.

Cordially,

Dave

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