Testimony by Paul Berg

Subcommittee on Science, Technology and Space

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Senator Stevenson, I am grateful for your invitation to participate in this committee's discussion of the current status of recombinant DNA activities. I particularly value the opportunity to present my views on the fundamental and practical issues that have been raised in the public debate on recombinant DNA methods.

To begin, let me introduce myself. My name is Paul Berg and I am Willson Professor of Biochemistry at Stanford University School of Medicine. When I'm not distracted by recombinant DNA matters I conduct research and teach biochemistry and molecular biology. My particular specialties are molecular genetics and viral carcinogenesis, both of which have become increasingly amenable to and dependent upon the use of recombinant DNA methods. I have neither a direct nor indirect association with any commercial enterprise engaged in, or contemplating, research or manufacture using recombinant DNA methods.

I am also not a newcomer to the recombinant DNA controversy. A moment will suffice to summarize the extent of my involvement. My laboratory was amongst the first to construct, outside of a living cell, a hybrid or recombinant DNA molecule; hence, I was one of the earliest practitioners of recombinant DNA research. Because several friends and colleagues expressed concern about the ramifications of my experiments I became an early participant in discussions of their potential risks. Subsequently, my involvement with these concerns grew by being chairman of a committee that warned the National Academy of Sciences about possible risks that might result from the indiscriminate use of recombinant DNA methods. I also served as chairman of the committee that convened and presided over the Asilomar Conference on Recombinant DNA Molecules; the report of those proceedings to the National Institutes of Health made specific and novel recommendations for scientific and administrative procedures that could ensure safe conduct of this line of research. Although not one of the architects of the NIH Guidelines, I was consulted at various times during their formulation and prior to their release in July, 1976.

A relevant question with which to begin is why are biologists throughout the world so excited by the recombinant DNA methodology. Is it, as some have charged, just fun and games, the chance to enhance one's career or ambitions or is it to advance genetic manipulation of humans for nefarious purposes? I doubt that any of these selfish reasons motivate more than a small fraction of the international scientific community. Rather, the overwhelming body of scientists view the recombinant DNA methodology as an extraordinary opportunity to solve important biological problems; the knowledge gained will illuminate our biologic nature and heritage; and very likely, help to alleviate the tragedies of human disease, starvation and the pollution of our environment. What are the opportunities, and important biological problems that recombinant DNA research can help to solve? Basically there are three answers:

1) The recombinant DNA methodology permits the isolation of single or groups of genes in high purity and virtually unlimited quantities from almost any living organism. Except in special cases this can not be accomplished by any other presently available method. Coupled with another new procedure, that is virtually child's play, the basic chemical structure of these isolated genes can be readily solved. These two techniques can tell us a great deal about the molecular structure and organization of the complex chromosomes of higher plants, animals and man. I described how recombinant DNA methods were uniquely suited for the task of reconstructing complex chromosomes during my presentation to the National Academy of Sciences Forum on Recombinant DNA Research last March. These are not idle speculations. They are realistic estimates drawn from the impressive achievements so far. There have also been problems and several surprises; each of the surprises introduces unexpected subtleties and makes more fascinating and urgent that we get on with their solution.

2) The ability to join together different DNA molecules permits the construction of new combinations or arrangements of genes

in simple as well as complex chromosomes. Together with classical methods for creating hybrid cells and organisms, one can envision more sophisticated analyses of the mechanism of gene and chromosome function. Understanding differentiation, the process whereby embryonic cells containing the identical complement of genes and chromosomes, gives rise to the myriad cells and organs of the organism, is a worthwhile and realizable goal. It is difficult for me to see how that knowledge will not have ramifications for the treatment and possibly prevention of certain birth defects and other developmental disorders.

3) The ability to isolate pure genes puts us at the threshold of new forms of medicine, industry and agriculture. Tailor-made organisms produced by recombinant DNA methods could provide valuable diagnostic reagents, probes for studying the operational status and efficiency of gene expression in health and disease, vaccines to immunize individuals and animals against the ravages of certain bacterial and viral infections and, possibly, even cancer; and, finally, there is extraordinary progress towards the construction of organisms that make therapeutically useful protein hormones; the isolation of the insulin gene is a promising start; the bacterial production of somatostatin, a hormone produced by the brain is even more astonishing. A joint effort between research groups at the University of California Medical Center, San Francisco, the City of Hope in Los Angeles and the Salk Institute in San Diego has resulted in the production of about 5 mg of somatostatin; only 100 gms of E.coli, grown in about 2 gallons of culture was needed. Bear in mind that it took nearly half a million sheep brains to yield 5 mg of somatostatin in the researches for which Drs. Guillemin and Schalley received this year's Nobel Prize in Medicine. Equally significant is the ingenious and elegant way in which it was accomplished: chemical synthesis of the gene and production of a modified form of the hormone so that chemical processing outside the organism is necessary to liberate the hormone. This approach provides a novel alternative to the previously planned procedures for producing many such products.

In this brief statement I can only mention but not amplify, some of the important advances that are being made by recombinant DNA techniques. If you like I could expand on some of them in the subsequent discussion. In short, I sense a mounting wave of accomplishment and progess that give lie to the charge that the benefits of recombinant DNA research are only speculative and ephemeral, and that only the dangers are real.

Before considering the question of risks I want to say a few words about genetic engineering, - the directed modification or even construction of new genetic constitutions for animals, plants and man. Partly because of the exaggerated and misleading claims by the popular press and some scientists and laymen as well, this term has evoked as much alarm as excitement. I would guess, that deep down it is what troubles some people most. But man has been involved actively in genetic engineering ever since he came down from the trees, planted maize and domesticated animals. The animals and plants that provide our food, the microorganisms that make our bread, beer and wine, the organisms that make our antibiotics and purify our sewage, are all subject to our genetic counseling. We have carried out wars of genocide against polio virus, small pox and plague and are much the better for it. Recall that for the worst holocaust in history Hitler did not need science and technology; ovens and gas chambers did the job. Malnutrition, poor and inadequate nutrition warps the minds and bodies of hundreds of millions of infants and children throughout the world and our personalities and behavior are manipulated and profoundly influenced by the printed page and television. Genetic manipulation, then, is not, itself, good or bad; we need to distinguish between the acquisition of knowledge and the applications of that knowledge and know how to achieve both wisely. Human genetic engineering is a concept worth examining in rational ways. It is not at all clear that it is feasible, nor when it will be, if at all. There are many difficult and contentious scientific, ethical and moral questions to be examined and at many stages there will be opportunities by all segments of our society to have their say. But preventing or slowing down basic genetic research now, seems ill-suited to dealing with that question.

Now let me turn to the matter of risks. Three years ago I expressed concern about the use of recombinant DNA techniques. There was no evidence that such experiments were hazardous, only conjecture; but we wanted assurance that these novel experiments would be safe. More than three years later, after considerable discussion by experts in this country and abroad and the analyses of past experiences and new findings, I and others have changed our assessment of the risks. I now believe that the possibility that experimental organisms will be hazardous or released is exceedingly small.

Where it has been examined, organisms modified by recombinant DNA methods are at a disadvantage in competing with their parental or wild organisms. Moreover, certain constructed DNA molecules, hitherto believed to be novel, can arise in nature by reactions akin to those used in the laboratory. There is also the virtually unanimous agreement of experts in infectious disease and epidemiology that strain K12, the enfeebled laboratory variant of E. coli widely used for recombinant DNA experiments, is unable to colonize normal human or animal intestinal tracts. Based on recent experiments and existing data, these experts also concluded that there is little or no likelihood that strain K12 can be transformed into an infectious or pathogenic organism or even into a human intestinal inhabitant by a bit of foreign DNA. This view has been echoed by Rene Dubos one of our most eminent biologists, an authority in infectious diseases and an ardent environmentalist. He concluded that "I doubt that gene recombination in the laboratory will create microbes more virulent than those endlessley created by natural processes". Moreover, the introduction of genetically enfeebled derivatives of strain K12 and vectors that are not readily transmissable to other bacteria, provide a further measure of safety. Hence, our initial concern that novel and laboratory-created recombinant DNA molecules could become widely disseminated to man, animals and the ecosystem is not supported by the available data.

Enacting legislation to govern the content and methods of scientific inquiry would be unprecedented and probably unworkable.

In my view legislation of the type that has so far been proposed would inhibit basic research on important biological and medical problems. The rules, procedures, and penalties are predicated on assumptions that will surely change, thereby making it difficult and cumbersome to adjust to the changing information, ideas and opportunities. I believe that legislation could stultify the creativity and initiative that has characterized the development of the recombinant DNA technique; it could also discourage and disillusion young scientists from entering this field. I believe that the present U.S. NIH guidelines, as well as analogous codes of practice in other countries, afford the security to meet the perceived risks. Many scientists believe the guidelines are too restrictive and that most of the proscriptions cannot be justified by any scientific information we now possess. But in spite of their reservations, scientists and their institutions have accepted the guidelines as an interim solution to the anxieties that remain. The acceptance of that view is a responsible action based on careful weighing of the alternatives and rejects irrational fears as a basis for decision.

As I see it, most of us are seeking the same objective: To reap the benefits, basic knowledge and practical advances from recombinant DNA research with a minimun of risk to our world. Members of the academic research community are now the principal practitioners of recombinant DNA research in this country. Since most of their research is funded by government agencies, it is being done in compliance with the procedures and administrative mechanisms embodied in the NIH Guidelines. The sanctions and consequences are severe and, therefore, a strong deterrent to noncompliance. A question frequently put is - what about recombinant DNA activities that are not under the Guidelines' jurisdiction? But surely there are existing mechanisms that guard the public against known hazards of pathogenic agents. Are there not existing statutes that could deal with these hypothetical risks as they do now with real and documented hazards? If not, we could consider establishing a parallel set of procedures and practices, agreed to by representatives of the private sector and monitored by the Department of Commerce, to guide industrial research, development and production activities using recombinant DNA methods? Industry's concerns in this area are unique to them; and the academic research community's concerns are foreign to the world of commerce. Does it make sense, then, to have both types of activity operate by an identical set of rules and procedures and subjected to constraints that are inappropriate to each? I suspect that just as the consortium of scientists, the public and the Department of HEW arrived at acceptable codes of practice, a similar coalition of the industrial sector, the public and the Department of Commerce could develop an equally acceptable set of guidelines for their activities.

Let me end by saying that I am particularly concerned by the growing efforts and influence of the anti-science forces. This is apparent in the increasing pressures to suppress scientists' explorations for fear of what their discoveries will uncover or produce. Decisions and agreements about what is desirable, acceptable and safe to know are nearly impossible to obtain at each level of social organization. Deeply held and conflicting sociopolitical ideals challenge the traditional views of what science is for and how it should be done. As these forces gain momentum, there are increasing attempts to restrict scientific research.

Society desperately requires effective mechanisms for anticipating and evaluating the impact of scientific and technologic breakthroughs. In the recombinant DNA matter scientists demonstrated that they could provide the early warning system for alerting society to the potential benefits and risks of their discoveries; accusations of self-interest, arrogance or even malevolence do little to encourage further efforts of that kind. We may already have squelched the concerned *scientist of tomorrow*. Governing bodies, everywhere, must seek better ways to encourage scientists' participation and the means to channel their input into the determination of policy.

Perhaps, these poetic words of Aristotle can guide us, scientists and politicians, in our search for wisdom in these matters.

He wrote:

> "The search for truth is in one way hard and in another easy. For it is evident that no one can master it fully nor miss it wholly. But each adds a little to our knowledge, and from all the facts assembled there arises a certain grandeur."

Thank you.