SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

HEARINGS

BEFORE THE

SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

NINETY-FIFTH CONGRESS

FIRST SESSION

MARCH 29, 30, 31; APRIL 27, 28; MAY 3, 4, 5, 25, 26;
SEPTEMBER 7 AND 8, 1977

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U.S. GOVERNMENT PRINTING OFFICE

93-481 O WASHINGTON : 1977

For sale by the Superintendent of Documents, U.S. Government Printing Office
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SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

TUESDAY, MARCH 29, 1977

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY,
Washington, D.C.

The subcommittee met, pursuant to adjournment, at 9:38 a.m. in room 2318, Rayburn House Office Building, Hon. Ray Thornton, (chairman of the subcommittee) presiding.

Chairman THORNTON. The hearing will come to order.

This morning the Subcommittee on Science, Research, and Technology begins its hearings on the science policy implications of the DNA recombinant molecule research issue. I have a prepared statement which I will insert in the record and then abbreviate my introductory remarks.

True science always stands upon a frontier. It probes at the edges of our knowledge and our ignorance, and we accept its contributions as valuable, its continuation as a necessity. Perceived as a gradual extension of the sphere of knowledge, science is accepted and praised as both our benefactor and our servant.

This is the science with which we are most comfortable, the science which explains how things work, which promises health, physical well-being, and material progress.

But the boundaries of the physical and biological sciences are not so easily contained. From time to time we find or come upon a field of inquiry which fundamentally challenges our concepts of life and nature, which confronts us too directly for our collective comfort or convenience, and yet intrigues us too greatly to ignore.

It is on this meeting ground of science and philosophy where man has made his greatest scientific advances. It's also here that science has caused its greatest strains upon our social, political, and religious institutions.

When Galileo offered the theory that the Earth revolves around the Sun, it was bad enough to his contemporaries that he committed scientific error. It was worse that he committed heresy as well.

Yet Galileo probed only the physical universe. As science has progressed and transformed our lives in so many ways, we have rejected many of the dogmas of an earlier day. And yet I suspect that many of us have harbored a feeling of security that there is at least one element of existence, the nature of life itself, that eludes scientific inquiry and control.

DNA research challenges that presumption as profoundly as Galileo challenged the science and religion of his day. It poses for the scientific community fundamental questions of its role in society. It poses for Government fundamental questions of its role in science.

The scientific community often resolves its own conflicts more easily than our political community can even understand them. Perhaps that will be the case here. But the scientific community cannot ignore the concerns of its larger constituency, and Government cannot isolate itself from the science that it has encouraged and supported.

Consideration of these questions brings us face to face with what I believe is one of the most fundamental issues before policymakers today: the issue of society interacting with science and the determination of the basic social responsibilities for the decisionmaking process.

Scientists are beginning to acknowledge the right of society to participate in decisions directly affecting the conduct of research, yet there is a strong belief in certain basic rights of scientific inquiry. The public is properly questioning the idea of total scientific freedom. The newly-acquired capability of manipulating the most fundamental processes of life has challenged society to think about the implications of this freedom.

But in order to understand the implications of DNA recombinant molecule research, we first have to understand the basic science involved, the potential risks and benefits of the research, and the actions which have been taken so far by the Federal Government and the governments of other nations.

In the April 25, 1953 issue of Nature, a modestly-written paper by James Watson and Francis Crick opened with the statement: "We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest." With this statement, James Watson and Francis Crick opened the doors to a new world of science.

The advances which have taken place since that time have been remarkable in terms of scientific progress, exceeding, in the opinion of many investigators, the developments in nuclear physics.

The Subcommittee on Science, Research and Technology, because of its jurisdiction over the broad area of science policy, had a particularly strong interest in this area of research, and in 1971 James Watson directed this committee's attention to the capabilities in molecular biology.

The committee prepared a study in 1972 which surveyed the status of this research. This study has been supplemented by two reports issued in 1974 and earlier in this year.

Since January of 1977, five bills plus a resolution have been introduced in the Congress to regulate such research. The House Subcommittee on Health and the Environment, chaired by our colleague Paul Rogers of Florida, held hearings on three of these bills 2 weeks ago. Senator Kennedy has announced a similar hearing for April 6.

But unlike these other congressional hearings which are directed toward specific legislative proposals, this subcommittee's interests deal more with the basic science policy questions. We wish to provide a forum in which we all may learn and discuss and even disagree—and be able to do this in an atmosphere which, we hope, is relatively free of prejudice, and devoid of hostility.

It is in this context that we've invited some of the most outstanding scientists in the United States to help us with this endeavor. We believe it's most appropriate to have the individual, who stated in the 1973 Gordon Conference on Nucleic Acids that "[these] experiments raise moral and ethical issues because of the potential hazards such [research] may engender," to lead off our hearings on this subject.

It is with great pleasure that I introduce Dr. Maxine Singer of the National Cancer Institute of the National Institutes of Health.

And I would like at this time to recognize the ranking minority member of the subcommittee, the gentleman from New Jersey, Mr. Hollenbeck, for such statement as he may wish to make.

Mr. HOLLENBECK. Thank you, Mr. Chairman.

Mr. Chairman, I'm hopeful that this series of hearings we begin today will help separate fact from fiction on recombinant DNA research now underway in the United States. It was only a generation ago that Watson and Crick made their discovery of the precise molecular structure of DNA, the substance which carries the determining hereditary chemicals or genes.

Since then, research on DNA has progressed almost at an exponential rate. The prospect of DNA recombinant molecule research or genetic engineering conjures up mixed feelings among the general public.

A large part of the dilemma facing most citizens is their honest desire to understand the benefits and hazards which surround the scientific endeavor without the distortion or theatrics which 30-second spot news features sometimes attain. Whatever the pros and cons of recombinant DNA research may be, the public's interest has been sparked and can only be satisfied by a thorough review of what this emerging science holds for us in the future.

The issue contains elements of both science per se and public policy. The purely scientific questions focus on the development of recombinant DNA research, what it offers in terms of improving the human condition, as well as agricultural applications. The apprehension lurking in the back of many persons' minds is that the same powerful technology which produces such genetic breakthroughs might one day backfire and cause irreparable harm to our environment or to the human race.

One purpose of these hearings is to try to shed light on whether such an apprehension is well-founded or is exaggerated. If the apprehension is well-founded, then the next step is to search for a means of containing any possible adverse reactions without jeopardizing our use of any beneficial applications of genetic engineering.

These considerations cause substantial public concern and require corresponding inquiry. The evidence presented during this series of hearings could shape the future direction of American policy on recombinant DNA research.

I'm sure, Mr. Chairman, that we are all looking forward to learning more about this intricate field in the coming months, such that we can make a well-informed contribution to legislative consideration in the future on the future of genetic engineering.

Thank you.

Chairman THORNTON. Thank you, Mr. Hollenbeck.

I'd like to ask you, Dr. Singer, to proceed now to give us your presentation. I understand this presentation precludes the use of a prepared statement, and I'm delighted to see the blackboard here.

After your presentation we'll hear from the other witnesses and then ask each of the witnesses to remain and act as a panel for questions by the members. And any of the members who cannot view the blackboard from this position are welcome to move on down.

Dr. Singer, without objection, I would like to include your statement from the National Academy Forum as part of the record.

[The material referred to, and a biographical sketch of Dr. Singer follows:]

Historical Perspective, Scientist Involvement

Talk by Maxine Singer, NAS Forum: Research with Recombinant DNA (March 7, 1977)

It is almost four years since the morning in New Hampshire, when as cochairman of the annual Gordon Conference on Nucleic Acids I said to my colleagues: "We all share the excitement and enthusiasm of yesterday morning's speaker who pointed out that the scientific developments reported then would permit interesting experiments involving the linking together of a variety of DNA molecules. The cause of the excitement is two fold. First, there is our fascination with an evolving understanding of these amazing molecules and their biological action and second, there is the idea that such manipulations may lead to useful tools for alleviation of human health problems. Nevertheless, we are all aware that such experiments raise moral and ethical issues because of the potential hazards such molecules may engender.....Because we are doing these experiments, and because we recognize the potential difficulties, we have a responsibility to concern ourselves with the safety of our coworkers and laboratory personnel as well as with the safety of the public. We are asked this morning to consider this responsibility."

As a result of the discussion and vote later that morning a letter was sent

to the Presidents of the National Academy of Sciences and Institute of Medicine from the participants in that meeting, some of whom were the pioneers in recombinant DNA research. That letter and its publication in SCIENCE Magazine, initiated a series of events of which this Forum is the latest. Perhaps most significant was the publication, in 1974, of the report of the Ad Hoc Committee on Recombinant Nucleic Acids, a group that included molecular biologists who were actively pursuing recombinant DNA work. Their report established certain precedents that have been central to all of the activities on recombinant DNA since that time. Thus, the report defined the possible hazards to include effects on human and non-human living things. The report called for an international discussion since the potential hazards could not be limited by national boundaries. The 1974 report recognized that the deliberations could not remain ad hoc but needed to be assumed by proper governmental bodies which represented the interests of society at large. The Ad Hoc committee recognized that, for reasons of safety, certain experiments ought not be done at least for the time being, and called for their colleagues around the world to join them in a deferral of those experiments. And finally, the committee established the precedent

that the discussion must be open and publicized.

Much of what has happened since 1974 has been in response to the requests made by the Ad Hoc group. The Asilomar conference in February 1975 was the first attempt, by an international group with varied expertise, to look at many types of recombinant DNA experiments and try to rank them as to potential danger. The Asilomar recommendations again advised that c rtain experiments ought not be carried out and, for other experiments, attempted to define levels of containment appropriate to the estimated risk.

In this country, the NIH alone among governmental organizations early assumed responsibility for serious and sustained consideration of the problem. The NIH effort resulted in the publication, in June 1976, of Guidelines for Research on Recombinant DNA. The NIH Guidelines are based on analyses that are similar to but more detailed, than, the Asilomar review and have explicit containment requirements for most technically feasible experiments.

Publication of the Guidelines was not, as some have implied, a "go' signal for all recombinant DNA research. Contrary to public belief, the voluntary deferral that started in the summer of 1974----it has been referred to as a

moratorium---did not call for a ban on all recombinant DNA research. Only two types of experiments were deferred: first, the construction of drug resistant or toxigenic microorganisms that do not occur naturally, and second, the introduction into bacterial cells of all or part of the genomes of viruses known to cause cancer in animals....at the present time there are no viruses known to cause cancer in humans. But there are many other types of recombinant DNA experiments that are feasible and important and their potential for hazard is not clearcut: they were not covered by the deferral. In the Asilomar recommendations and in the NIH Guidelines, the experiments deferred in 1974 either remain proscribed or can be performed only under extremely stringent containment measures. The Guidelines forbid additional experiments, including many that have provoked great fear of the possible hazards of recombinant DNA research in the mind of the public. From July of 1974 until Asilomar in February of 1975 and from then until the publication of the Guidelines in June 1976 there was, as far as can be learned, complete compliance with the then governing prohibitions and containment recommendations. Experiments that were not prohibited were carried out during the entire period. There is,

thus far, no indication that hazardous organisms have resulted from any of the experiments. Indeed, with the exception of certain experiments involving antibiotic resistance and toxins, we still do not know that hazardous organisms can in fact be produced from recombinant DNA experiments. We cannot accurately describe the probability of, or the precise nature of the conjectured hazards. Statements implying that uncontrollable epidemic or environmental disaster is a certainty are as misleading and useless as statements implying that no possible hazard can come from the experiments. Insufficient knowledge is the reason why the public is faced with a range of different opinions from within the scientific community. Insufficient knowledge is also the reason why the recommendations in the NIH Guidelines were necessarily based on judgment and consensus.

The adequacy of the containment requirements mandated by the NIH Guidelines for permissible experiments is a useful focus for discussion. In this way the very different issues raised by different experiments can be considered. Misleading and sweeping statements referring to all recombinant DNA experiments can be avoided. Most scientists and laymen who have studied

the situation agree that certain recombinant DNA experiments which mimic naturally occurring processes are without unique potential for harm. Most people agree that certain other experiments ought not be done at all at the present time. The facile description of people as either "proponents" or "opponents" belies broad areas of agreement as well as the complexity of the issues. Similarly, the facile description of bacteria containing recombined DNA from a foreign source as "new living things" is misleading. A bacteral cell normally contains thousands of genes each of which contributes to the nature of the cell in interdependent ways. The introduction of one or a few new foreign genes to this complex system may be able to alter certain properties of the cell- but the bacteria basically remains its old self.

Questions do remain about certain specific recommendations in the Guidelines, and the need for additional or different provisions is a subject of debate. The current controversy over whether or not recombinant DNA experiments may cause long-term evolutionary consequences is properly part of the debate on the provisions of the Guidelines since the risks are imagined to result from a particular type of recombinant DNA experiment.

Debate aside, there has been substantial endorsement of the NIH Guidelines both within the scientific community and by responsible representative public bodies including the Cambridge City Council, the University of Michigan Regents, and the Senate Subcommittee on Health. All work supported by federal government funds is now covered by the Guidelines. The Guidelines are viewed as mandatory by grantees and grantors. The threat of removal of research support is a powerful sanction not a trivial one. Institutional Biohazards Committees are functioning at grantee institutions and at NIH. Reports from the Committees indicate a diligent and serious commitment to the provisions of the Guidelines. Most dramatic evidence of this compliance comes from the willing destruction of materials constructed in accordance with the Asilomar recommendations but prohibited by the NIH Guidelines and from the straightforward discussions of risk and containment now appearing in published scientific papers.

There remains an urgent need to extend the provisions of the Guidelines in an enforceable manner to work carried out with non-Federal funds. The NIH does not have such enforcement authority and, as a principal research sponsor, is not an appropriate agency for such a task. Intensive Federal efforts to

find suitable enforcement mechanisms are nearing completion and we may expect to hear about these efforts this week. Discussion is also proceeding actively in several State and local governments.

The current situation in the United States is but one aspect of world-wide attention to this problem. The scientific community, working through its extensive international collegial network, sought and obtained official attention to the problem of recombinant DNA in many countries. Two countries, Canada and the United Kingdom, have independently developed guidelines and although they differ in detail from one another and from the American guidelines all three agree in general approach and, to a large extent, in the assessments of relative risk. Other countries will make use of one or another of these sets of guidelines, organizing the implementation of them in ways appropriate to national conditions. Several international organizations...on the official governmental level, the World Health Organization and on the scientific level, the European Molecular Biology Organization and the International Council of Scientific Unions have active programs designed to foster both science and safety by collection and dispersal of information and by training of investigators.

Scientific progress with recombinant DNA techniques has been slow. Meeting the requirements of the guidelines...from prior approval and certification before initiating experiments to the demanding containment requirements----- has slowed the pace of work. Certain permissible experiments are not presently feasible because of the lack of required physical facilities, or the lack of appropriate certified hosts and vectors. The Committee advising the director of NIH on certification of biologically contained hosts and vectors has been rigorous in its evaluations.

This slow-down is useful. It allows time for prudent evaluation of the accumulating experimental results and the implications of those results relevant to potential hazards. The slow-down is also frustrating-not only because it has delayed acquisition of information, but also because research is a creative as well as a technical endeavor. In successful, innovative work the impetus of enthusiasm, of acting quickly upon an exciting idea, is undeniable.

As I mentioned before, certain recombinant DNA research has continued during the last few years. Those experiments have confirmed the initial enthusiasm for the value of the method.

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It is now known that the DNA of higher organisms, from yeast to mammals, can be faithfully reproduced in bacterial cells and,...DNA of bacterial origin is readily reproduced in animal cells growing as single cells in tissue culture. Thus the promise of the method for the preparation of useful and otherwise unobtainable quantities of specific DNA fragments or genes is an established fact.

Transcription of the information encoded in DNA into RNA is the first chemical step in genetic expression. We now know that the DNA of complex organisms can also be transcribed into RNA inside bacteria. And, similarly, the DNA of simple organisms can be transcribed into RNA in cells derived from complex organisms. Detailed study of these systems promises the elucidation of important questions concerning the control of genetic expression.

The final step in gene expression is the translation of the information in the RNA that results in the formation of a protein. Ultimately it is the set of proteins unique to each organism that define the recognizable properties of each species and individual. Proteins encoded by the DNA of yeast, a primitive form of higher organism, are synthesized and are active

in bacterial cells. These results indicate that some initially speculative practical applications of recombinant DNA techniques will be realizable.

Taken altogether these results confirm the unity of nature both in structure and function.

It was not easy for the scientific community to raise the issues implicit in recombinant DNA research. The actions involved significant divergence from historical practice and belief. The actors were unaccustomed to consensual undertakings and the wisest course was not clear. Doubts still persist about the wisdom of each step that was taken. Those colleagues who warned that uncontainable and irrational public responses might follow were correct. But their counsel was set aside because other considerations were overriding. It is worth making these other considerations explicit.

Scientists today recognize their responsibility to the public that supports scientific work in the expectation that the results will have a significant positive impact on society. To describe the scientific community of the late twentieth century otherwise is to ignore or misunderstand the

evidence. Dispute over the best way to exercise that responsibility must not be confused with a negation of it. The scientific community has accepted the counsel of ethicists, philosophers and representatives of the public who long troubled to point out this responsibility. Origins for the actions regarding recombinant DNA are also found in the worldwide movement to protect the biosphere from the ravages of technological development. And again, while we need continuing discussion of the proper balance between efforts to ensure environmental protection and opportunities for solutions to existing and forthcoming problems, we all agree about the importance of environmental considerations.

Scientists also accept the need to restrict certain laboratory practices in order to protect the safety and health of laboratory workers and the public. Further, we recognize the need to consider possible hazards before large scale activity is undertaken and before untoward events occur. But we differentiate between restrictions on hazardous or potentially hazardous activities and restrictions on intellectual freedom. While a democratic society rests on the virtually absolute freedom of individuals to ask any question whatever,

it is clearly unacceptable knowingly to cause harm to others in the process of trying to obtain an answer. Thus the recombinant DNA problem was originally posed and has been dealt with as a problem in the safety of living things.

Some have argued that this definition of the problem was too narrow. It is said that scientists and the public should consider the moral and ethical implications of future applications of the knowledge to be acquired from this research. And so they should....but in broader contexts and with even wider participation than was engaged in dealing with the technical matters of safety and laboratory practice.

Further, it has been argued that scientists should not only consider-but should in fact assume responsibility for-the eventual application of any knowledge they may acquire in the course of research. That statement raises complex and difficult issues-and varied responses. It can be a subject for reasonable debate only if the distinction between acquisition of knowledge and application of knowledge is not obscured. Thus, any exercise of such responsibility can logically come only after the acquisition of the knowledge: to call for such an exercise prior to the research itself is a sham because

the outcome of the research is, by definition, not knowable in advance. This is not to say that freedom of inquiry is unlimited - but limitations on the acquisition of knowledge must be with good cause - as when harm may result from the process of acquisition. History reminds us that constant vigilance is required if we are to avoid the perilous consequences of attempts by society or individuals to determine what is permissible to know and what is illicit to learn. The consequences of attempts to restrain the search for knowledge have been even more fearsome than the science fiction scenarios constructed by genetic fear-mongers.

Besides, such attempts are certain to fail. They will fail, first, because we are not smart enough to foresee what we will or will not learn from a given line of research. They will fail, secondly, because we are not smart enough to foresee all the future applications of the knowledge. They will fail, finally, because the indomitable forces of nature oppose such attempts...the acquisition of knowledge by the human brain is part of protean nature....biologists and poets alike know this.

Emily Dickinson wrote in 1862:

> The Brain is just the weight of God
> For--Heft them----pound for pound
> And they will differ...If they do...
> As Syllable from Sound.

Most scientists today also recognize the need to participate, together with the public, in decisions about research areas ripe for encouragement or areas where knowledge is desired, or areas in which safeguards may be needed. The worthy report of the Cambridge Experimentation Review Board must surely quiet doubts about the ability of the lay public to deal intelligently and forthrightly with complex technical issues. Future public reviews of such matters will be judged against the standard set by that Cambridge Review Board. But cooperative deliberations between scientists and public bodies is difficult because scientists have not educated others adequately in the past. It should not then be surprising if deep fears and ambiguities arise in the minds and hearts of those who suddenly learn the depths of modern insights into the nature of living things. On the other hand, those responsible for making public policy should recognize that levels of anxiety are often unrelated to levels of risk. A continuing search for effective means to inform and educate the public about science is essential.

The history of the debate over recombinant DNA suggests that current means give erratic results. Press coverage of the Asilomar conference in February of 1975 was excellent. As public discussion broadens, however, we encounter serious problems in the presentation of the issues and the science to the public. Communication between scientists and the public is often impeded by writers or TV producers who unfortunately take it upon themselves to determine what the public needs to know or what the public can understand. The public is the loser as they are inadequately or incorrectly informed. And serious ethical considerations confound the scientist if his efforts to cooperate with the media are used to misinform or needlessly frighten.

For the future, scientists need to continue, together with federal and local governments, to evolve policies that offer protection from potential hazards and preserve opportunities for discovery and development of safe and desirable applications. Scientists must share their insights into the nature of living things with increasing numbers of people so that debate can be predicated on understanding rather than fear. In order to counteract the growing pessimism about the nature of knowledge, the proper separation of

science from technology must be made and, in the continuing dialog, the distinct values and problems inherent in each must be carefully articulated. Finally if scientists commit themselves to their unique opportunities to serve as an early warning system, society can proceed with prudence and caution as scientific knowledge grows.

MAXINE SINGER

Maxine Singer was born in New York City in 1931. She received the A.B. degree with High Honors from Swarthmore College in 1952 and the Ph.D. degree (Biochemistry) from Yale University in 1957; in 1977 she received the Doctor of Science from Wesleyan University. After a period as a U.S. Public Health Service Postdoctoral Fellow at the National Institutes of Health she joined the staff of the National Institute of Arthritis and Metabolic Diseases in 1958 as a Research Chemist. In 1974 she became Head, Section on Nucleic Acid Enzymology, Division of Cancer Biology and Diagnosis, National Cancer Institute.

She is a member of the American Society of Biological Chemists, Inc., as well as several other scientific societies. She served from 1968–1974 as a member of the Editorial Board of the Journal of Biological Chemistry and from 1971 to the present as a member of the Editorial Board of SCIENCE Magazine. From 1972 to 1975 she was a member of the Board of Trustees, Wesleyan University, Connecticut. She is currently a fellow (trustee) of the Yale (University) Corporation. She was a member of the Organizing Committee, Asilomar Conference on Recombinant DNA Molecules (February 1975).

She is the author or coauthor of over 60 scientific papers. Her work for many years concentrated on the structure and enzymology of ribosenucleic acid (RNA). More recently work in her laboratory has been concerned with the small DNA virus 40, and the structure of the DNA present in defective forms of the viral genome as well as with the organization of mammalian DNA and the structure of chromatin.

Maxine Singer is married and resides in the District of Columbia with her husband and their four children.

STATEMENT OF DR. MAXINE SINGER, LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, BETHESDA

Dr. SINGER. Thank you, Mr. Thornton, and thank you all for your invitation to me to come this morning and talk about the science.

I think that I agree with your statement that it's very imporant in considering the public policy matters that all of the people who are interested in recombinant DNA have some understanding of the science, and it isn't very difficult, although we sometimes talk as though it is. It's a pleasure to introduce you all to some of this.

Can you see this? Mr. Glickman?

Mr. GLICKMAN. Could you turn it a little?

Dr. SINGER. The basic fact is that every living cell, whether it be a cell that lives by itself as a single cell, or whether it be a cell that's part of some larger organism, contains within it all of the information that that cell or the whole organism needs to carry out all of the processes that make it itself, that allow it to eat, that allow it to grow, that allow it to reproduce its own kind. Basically, genetics is a study of information and the way information is held in living things and the way it's used.

Every cell has all of the information, but not every cell needs all of the information at any one time. So this complex information system, in addition to carrying information, also need to have the ability to control the use of it. It needs to turn on certain information at certain times in the life of the cell and turn it off at other times. Those times may be part of the regular progress of development, as when a fish develops from a fertilized egg. Or those times may be in response to certain environmental needs which say that the cell must have certain functions at a particular moment and therefore it must

turn them on; and later on, when it doesn't require these functions, it should turn them off again.

Now, this is a general description of an information system in living things. But the work of the last 20 years, starting with that of Watson and Crick, has permitted us to be able to describe this information system in chemical terms, that is, in terms of the molecules involved. The most central molecule is the molecule that's called DNA, which is simply an abbreviation for the very long word deoxyribose nucleic acid.

It is this molecule which is the respository of all of the information in every cell, which allows the cell to carry out whatever functions are necessary at whatever times they are necessary. It's a very long molecule; it's very complicated molecule. It can be described as the very famous double helix of Watson and Crick.

I think it's probably more useful for us to look at this helix as a straight line. The reason for that is that the information in the DNA molecule is arranged in a linear fashion, just like a sentence in a book. So we can look upon the DNA molecule as a long straight line, remembering that in reality it's a complex double helix and that every cell has a DNA molecule of its own type. This single cell, a bacteria cell for example, has a DNA molecule specifically for itself and this fish also has a DNA molecule specifically for itself.

We've come to know a great deal about the way the information system of DNA operates and are able to describe it in some chemical detail. For small bacteria which have a relatively small DNA molecule, say about a millimeter in length, we have even come to know something about the way the on-off switches operate, in terms of turning on genes when you need them and turning them off at other times.

But the DNA from complex organisms is many times as long as that. It's about a meter long instead of 1 millimeter, and it is much more complicated. In fact, we don't know a great deal about the way the molecule operates and the way the controls for the on-off switches operate, or anything of that sort. This is one of the things that gives impetus to the desire to use recombinant DNA methods, because it does permit the study of these much more complicated molecules.

In a bacteria cell, as well as in the cells of more complex organisms, there are also very often smaller DNA molecules that are carried along as separate inclusions—and I have drawn them as circles because they are very often circular in shape. These DNA molecules may be what are known as plasmids, or they may be DNA molecules that contain the genes of a particular virus that lives as a parasite in the cell. These are also important in recombinant DNA technology.

I brought along these beads, because they're a favorite tool of molecular biologists [indicating pop-it beads]. They may seem silly, but this really does enable us to obtain a very good idea of what a DNA molecule would look like.

Say that this is the DNA molecule from this fish. It's about a meter long and each of the beads represent a gene—the red beads represent one kind of a set of genes, the green beads another set of genes, and the yellow beads that appear every once in awhile represent control signals; that is, they are the signals that are built into this information system that say turn on this group of genes and let them be expressed,

and then, at a later time when they are no longer needed, this signal says turn them off.

It's this kind of complicated system of control that we would like to study. But because it's so long it's very, very difficult.

Now, the small inclusion bodies are represented by a small circular DNA molecule of this sort, and they are easier to manipulate. Physically, it's easier to isolate them from a cell; that is, it's relatively easy to take them out of the bacteria cell and prepare them in quite pure form in the laboratory. When I say "easy" I mean easy for us in a technical way, but it requires a number of complicated procedures and complex machinery as well. But it can be done.

One of the most important things about such DNA molecules, in addition to the fact that they carry their own genes, is that they have a particular area in the molecule which is responsible for the fact that this small inclusion body, or plasmid, can actually reproduce itself in the cell. And it's because it can reproduce itself that it's so useful for recombinant experiments, as I will try and explain.

Now, basically, what you do in a recombinant experiment is to isolate such small DNA molecules and then, by a very special technique with an enzyme, you break them. It was the discovery and purification of a certain group of enzymes that permits one to break a DNA molecule at a particular place that really opened up a great number of the possibilities for recombination experiments. The DNA, which is in a very small amount of solution, is mixed with a small amount of enzyme, and the enzyme opens the DNA at this very particular place.

It's also possible to isolate the large DNA from a complex organism, but it is so big and fragile that you usually get it out in very large pieces. And then one can use the same enzyme as before to make them into smaller pieces which have very particular kinds of ends due to the manner in which the enzyme cleaves the fragments of the molecule.

If we cleaved the DNA molecules so that the ends fit together, as they do in this kind of experiment, it is possible to join them together. This again involves certain biochemical procedures which are well known and relatively straightforward in the laboratory.

So now we've taken a plasmid which came, in this instance, from a bacterial cell, and we've added to it a piece of DNA that came from a fish. This is called a recombinant DNA molecule. By itself, however, it's not very useful.

What makes this molecule extremely useful is that it can be put back into a cell of the same sort from which the original plasmid DNA was derived and this new molecule can be reproduced. Every time this cell divides, each new cell will contain the original DNA of the cell and it will now also have this small inclusion that has the recombined DNA in it. If we grow out many generations of such cells—which we can do in a few hours in the laboratory—we now have made large quantities of a piece of DNA from a fish, a piece which represented one one-millionth of the DNA from a fish, a piece which represented one one-millionth of the DNA that was in here originally, and which we would have had no other way to isolate in a pure form.

We can now take the recombinant DNA molecules out of the cells, purify them in the same way we did originally, and use the same enzymes to excise the pieces of fish DNA. The result is that we now have a chemically clean, well-characterized piece of DNA to study.

I've left out certain problems along the way, but this is a general view of the process.

The discoveries which were crucial to developing this technology came in the early part of this decade. One was the discovery of these very special enzymes, which allow one to split molecules so that they have special kinds of ends which can be stuck back together again. Another crucial finding was the discovery of ways to take such small recombined molecules and put them back into a large bacterial cell.

These two findings were really the two things that came together to permit these experiments. There are now other ways of doing things, and there are modifications which allow you to do slightly different things. But basically, the methods are the same.

One of the questions I was asked to address was: What are the alternative methods of doing these kinds of experiments? In order to do that, I think first I should list for you what you can do by these experiments. And then we can ask whether there are other ways to achieve the same results.

The first thing, as I mentioned before, is that you can isolate and study small pieces of DNA corresponding to one bit of genetic information. This single bit is called a gene, and the study of the chemical structure of that gene is now made possible. One is enabled to study not only the normal structure, but also the structure of a gene which has mutated or changed and therefore does not function as well as the normal gene.

Another thing that one can now do is to isolate the switches that turn the gene on at the beginning of the readout of this information sequence and turn it off at the end. One would then be in a position to study the control mechanisms, control mechanisms which are believed to be operative in the way hormones act in cells, the way cells of complex organisms respond to different environmental situations, or the way the normal progress of development occurs. Knowledge of the chemical nature of these switches is of extreme importance.

If this recombined molecule is in the bacterial cell and it has the gene from, for example, the fish, then it's possible that this genetic information, this gene from the fish, will actually be expressed. That is, the information stored in the gene will be used in this bacterial cell to make a particular product called a protein. Therefore, one could study the manner in which this fish protein is made in a very isolated situation, something we could never do in a whole fish.

So, these are the three kinds of things that one can do: Study the structure of the gene; study the nature of the control mechanisms that switch genes on and off; and, study the manner in which proteins are made in a cell.

The question then is whether there are any other ways to study these things. Well, in studying bacteria there are alternative methods for some of these kinds of questions and, in fact, it is those alternative methods which have been used in the past 20 years to develop our very extensive knowledge of genetics. Because of the complexity of higher organisms, however, most studies have been restricted to bacteria. And, in fact, it's important to recognize that we really don't know how genes work in complicated organisms. We make a very big theoretical jump from what we've learned about bacteria to say that complicated organisms work more or less the same way. There

are good reasons for making this jump, but it nevertheless is a jump with many assumptions built into it. No other way to study these aspects of complicated organisms is apparent at the present moment or the foreseeable future.

Some people have maintained that it is possible to study the chemistry and the structure of a gene by manufacturing it in the laboratory, by synthesizing it. This might seem possible, since this year the really extraordinary feat of synthesizing a bacterial gene just from simple chemicals was accomplished by Prof. Gobind Khorana at the Massachusetts Institute of Technology. He constructed the entire sequence of a gene. It took 9 years. Now, that's one problem—that it takes a long time. But that's a minor problem, because in order to synthesize the structure he had to know what the structure was to begin with. Otherwise he could never have done it. And there is no way to know a structure unless you can first isolate the gene in pure form—a feature which we currently have no way to do for complex organisms except by means of recombinant DNA technology.

It has also been suggested that one could do some of the things done by recombinant technology by means of RNA/DNA conversion. I mentioned previously that the genes, that is the DNA, are expressed in a cell, in most instances, by making a particular protein. It is, in fact, the nature of the proteins, or the accumulated nature of the various proteins in any organism, that make the organism look and behave the way it does.

But in the actual readout mechanism from a gene, in the decoding of this information ultimately into the synthesis of proteins, there is an intermediate step, which involves the synthesis of another nucleic acid similar to DNA but called RNA. It has become possible in recent years to isolate, in certain instances, quite pure RNA molecules, which are really copies of certain genes, and to convert them back into a DNA copy by chemical and other methods.

Some people have advocated the use of this DNA rather than recombinant technology. The trouble with this is twofold. First of all, there are only very special instances in which it is possible to isolate a pure RNA and then make a DNA copy of it. There are very special situations in living things in which cells become highly specialized and make only one protein and, therefore, have only one RNA. An example would be red blood cells. Basically the only protein they make is hemoglobin, and so it's very easy to isolate from red blood cells the RNA that contains the information for making the protein globin, make a DNA copy and study the structure of the DNA.

But most proteins and most processes in living things occur in a much more complex milieu of many proteins being synthesized. So that's one problem with this method.

The second problem is that when the RNA is made in the cell, only the RNA that is needed for making the protein is available. The on-off switches, which are of such great interest, have been lost. Therefore, the DNA copy, which is made from the globin RNA, no longer has these switches and we are not able to study the most important questions from the point of view of disease processes; namely, the nature of the control mechanisms.

Those are the reasons why the alternative methods that have been suggested really do not give us the same capability as does recombinant technology.

I'll stop there, Mr. Thornton.

CHAIRMAN THORNTON. Thank you very much, Dr. Singer, for a very excellent presentation. We will proceed to hear from the other witnesses and reserve our questions until we can ask them of the panel.

Some people are very concerned about the possibility of a recombined DNA molecule might escape from a laboratory and contaminate the environment. There are a couple of scientific methods which are presently being employed to keep this from happening, one being physical containment and the other being alteration of the makeup of the gene itself, the molecule itself.

To speak about the first of these, the physical containment, we're pleased to have with us today Dr. Emmett Barkley, who is the Director of the Office of Research Safety for the National Cancer Institute, NIH, Bethesda.

Dr. Barkley.

[A biographical sketch of Dr. Barkley follows:]

Responsible for operating the National Cancer Institutes' virus containment facility and prototype laboratories, providing research support services to resident investigators of these laboratories.

Supervises the work of seventeen National Cancer Institue employees and twelve contract employees including four engineers and three microbiologists.

1965-1967 Graduate education at the University of Minnesota. Academic emphasis was in mechanical engineering, environmental health, biometry, and microbiology. Academic program was designed to provide a strong foundation in the biomedical sciences and a complete understanding of Public Health, while continuing to strengthen engineering background.

1964-1965 Staff Engineer, Field Studies, National Cancer Institute, NIH, PHS, DHEW.

Responsible for defining engineering criteria for biomedical projects requiring engineering support. Assisted in developing institute program for determining biohazards related to cancer research and establishing organization for conducting biohazards control and containment research and development.

1963-1964 Liaison Engineer, Division of Research Services, NIH, PHS,DHEW.

Responsible for assisting the biomedical staff of the National Cancer Institute in its inter-relationships with the Division of Research Services. Defined engineering criteria and presented these criteria to engineering staff of the Division of Research Services.

1961-1963 Staff Engineer, Water Supply and Pollution Control, PHS, DHEW, Region IX, San Francisco, California.

Developed programs and technical reports on water resources projects in State of California. In charge of water resource analysis of San Joaquin River Valley. This project included evaluation of water pollution potentials, area water resource requirements, economic studies and the development of recommendations for improving water quality and increasing water use. Responsible for maintaining water pollution inventories for State areas. Performed field stream pollution surveys, including chemical, physical and biological analysis. Computed economic benefits for various water resource development projects.

1961 Staff Engineer, Water Supply and Pollution Control, PHS, DHEW, Region III, Charlottesville, Virginia.

Responsible for the evaluation of design criteria and review of engineering plans and specifications of sewage treatment plants which were supported in part by Federal grants under the Construction Grants program.

Professional Society Memberships:

American Public Health Association
Commissioned Officers Association
American Association for the Advancement of Science

Porfessional Honors and Awards:

Technical Program Chairman, American Association of Contamination Control, 1968 - 1969.

Consultant, International Agency for Research on Cancer, Lyon, France, February 1970.

Consultant, American Institute of Biological Sciences, Study: The Role of the Lunar Receiving Laboratory in Post-Appolo Biological and Biomedical Activities. Member Study Group I: Application Involving Microbiological Containment Technology. 1970.

Vice Chairman, Biohazards Control and Containment Segment, Special Virus Cancer Program, National Cancer Institute 1968 - 1970.

DHEW, PHS Commendation Medal, 1972. For defining the engineering criteria for biomedical programs and concepts that led to the establishment of the Biohazards Control and Containment Segment of the National Cancer Institute's Special Virus Cancer Program.

Lecturer; Principals of Biohazard and Injury Control for the Biomedical Laboratory, 1972 - 1975.

Outside Service Training, PHS, University of Minnesota, 1965 - 1967.

Member, DHEW Toxicology Subcommittee for Carcinogen Standards, 1974.

Chairman, NIH Biohazard Committee, 1974.

Chairman, Cancer Research Safety Committee, 1974.

Chairman, Laboratory Chemical Carcinogen Safety Standards Subcommittee of the DHEW Committee to Coordinate Toxicology and Related Programs 1975.

Consultant; Recombinant DNA Molecules Program Advisory Committee, 1975.

Adjunct member of the facility, W. Alton Jones Cell Science Center, Lake Placid, New York, 1975.

Technical Presentations:

Contamination Control - The Architect, The Engineer and the Uses, 7th Annual Technical Meeting, American Association for Contamination Control, Chicago, Illinois, May 13, 1968.

Open Isolation Systems - Care of Low Resistance Hospital Patients, Symposium on Laminar Air Flow Systems Federated Medical Resources, Camden, N.J. January 16, 1969.

Principal Limitations of Laminar Flow for Care of Low Resistance Patients, 1969 Annual Meeting of the Society for Industrial Microbiology, Burlington, Vt., August 21, 1969.

Development of a Concept for Virus Containment, National Safety Congress and Exposition, National Safety Council, Chicago, Illinois, October 30, 1969.

Evidence of Successful Use of Laminar Air Flow Systems in Medical Research, Laminar Air Flow Seminar, Veterans Administration, Washington, D.C., April 6, 1970.

A New Era of Biological Safety Cabinets, X International Congress for Microbiology, Mexico City, Mexico, August 13, 1970.

The Effective Use of Procedures, Equipment and Facilities for Biohazard Control, American Society of Microbiology, Philadelphia, Pennsylvania, April 25, 1972.

Deficiencies and Limitations of Laminar Flow Safety Cabinets, 15th Biological Safety Conference, Bethesda, Maryland, October 10-12, 1972.

Environmental Control in Oncogenic Virus Research, Environmental Physiology Seminar, John B. Pierce Foundation Laboratory, New Haven, Conn., December 4, 1972.

Principles of Biohazard Control in Cancer Virus Research, 6th International Symposium on Comparative Leukemia Research, Japan, September 16-21, 1973.

The Impact of the Emergency Standard on Certain Carcinogens in Animal Bioassay Studies, 24th American Association for Laboratory Animal Science, Bal Harbour, Miami Beach, Florida, October 1-5, 1973.

The Development of a General Purpose Laminar Flow Biological Safety Cabinet, 16th Biological Safety Conference, Ames, Iowa, October 16-18, 1973.

Is Personnel Safety the Forgotten Objective of the Laminar Flow Era?, AACC Meeting, Norristown, Penn., January 22, 1974.

Air Conditioning for Particulate Control in Industrial Processes, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc., Los Angeles, Calif., January 29-February 1, 1974.

The Treatment of Exhaust Air From Cancer Research Laboratories, AIChE 76th National Meeting, Tulsa, Oklahoma, March 10-13, 1974.

Minimum Safety Guidelines for Research in Cancer, Symposium on Chemicals and Cancer, Rochester, New York, May 7-8 1974.

Controls for Safe Handling of Chemical Carcinogens in Laboratories, 168th ACS National Meeting, Atlantic City, New Jersey, September 10, 1974.

Minimum Safety Guidelines for Research in Cancer, Annual National Safety Congress and Exposition, Chicago, Illinois, September 30-October 2, 1974.

Approaches for the Control of Chemical Carcinogens in the Research Laboratory, 1974 Meeting of the Tennessee Valley Section of the Industrial Hygiene Association, Gatlinberg, Tennessee, October 9-10, 1974.

The Synthesis of a Relevant Cancer Research Safety Policy, 17th Biological Safety Conference, Becton, Dickinson and Company Research Center, Research Triangle Park, North Carolina, October 15-17, 1974.

Epidemiology of Laboratory-Acquired Infections, American Industrial Hygiene Association Annual Meeting, Minneapolis, Minnesota, June 2, 1975.

OSHA Regulations/DHEW Standards for Safety in Carcinogenesis Research, Third Annual Collaborative Conference, Orlando, Florida February 2-5, 1975.

Publications:

Reviewer, Microbiological Contamination Control Facilities, Van Nostrand Reinhold Company, New York City, New York, 1969, Edited by Runkle and Phillips.

Wedum, A. G., Barkley, W. E. and Hellman, A., Handling of Infectious Agents, J. Amer. Vet. Med. Assoc. Vol. 161:11, 1557-1567, 1972.

Barkley, W. E., Facilities and Equipment for Virus Containment. Biohazards in Biological Research, Ed., Hellman, A., Oxman, M.N., and Pollack, R. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, p. 327, 1973.

Barkley, W. E. and Henke, C. B., Exhaust Air Treatment in Cancer Research Facilities, AIChE Symposium Series, New York, New York, AIChE 76th National Meeting, Tulsa, Oklahoma, March 11, 1974.

Chatigny, M. A., Barkley, W. E. and Vogl, W. A., Aerosol Biohazard in Microbiological Laboratories and How It Is Affected by Air Conditioning Systems, ASHRAE Transactions 1974, Vol. 80, Part 1.

STATEMENT OF DR. EMMETT BARKLEY, DIRECTOR, OFFICE OF RESEARCH SAFETY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, BETHESDA

Dr. BARKLEY. Thank you, Mr. Thornton.

I appreciate the opportunity to appear before you today to discuss physical containment as it relates to recombinant DNA research. I would like to begin by reviewing my professional background.

I am a civil engineer. My graduate training is in environmental health and microbiology. I have worked in the field of biological safety for 12 years. I have been privileged to have worked with the late Dr. Arnold Wedum who, as director of safety at Fort Detrick, was singularly responsible for the promotion and advancement of the field of biological safety.

My research interests have been of an applied nature. I have developed physical containment systems that are extensively used in microbiological laboratories today. Most recently, I have been involved in the development of laboratory safety programs within the National Cancer Institute. I also serve as the chairperson of the Biohazards Committee at the National Institutes of Health.

Now I will discuss the physical containment safeguards that are to be used in recombinant DNA research. The objectives of physical containment is to confine microorganisms containing recombinant DNA molecules to the research environment. The purpose of physical containment is to reduce the potential for exposure of the laboratory worker, persons outside of the laboratory, and the environment to recombinant DNA materials.

The NIH guidelines for recombinant DNA research describe four levels of physical containment which are referred to as P1, P2, P3, and P4. The least potentially hazardous experiments are conducted using P1 safeguards, and those requiring the greatest restrictions are conducted using P4 safeguards.

The four levels of physical containment are based on recommended methods for the safe handling of microorganisms that produce human disease of varying degrees of severity. For example, the P4 level safeguards are appropriate for the containment of either microorganisms that are extremely hazardous to laboratory personnel, such as Marburg virus, or those that may cause serious epidemic disease, such as smallpox virus.

Physical containment is achieved through the use of laboratory practices, containment equipment, and facility safeguards. Emphasis is placed on primary means of physical containment which are provided by laboratory practices and containment equipment. Facility safeguards provide a secondary means of protection against the accidental release of microorganisms outside the laboratory or to the environment. These safeguards are most extensively used in facilities in which experiments of high potential hazard are to be performed.

At the P1 level, physical containment is provided by standard microbiological practices. These include aseptic techniques, the daily decontamination of work surfaces, the decontamination of contaminated liquid and solid wastes, the use of safe pipefitting procedures, and the observance of appropriate worker hygienic procedures.

Physical containment at the P2 level is provided by a combination of the practices just mentioned and containment equipment. In addition to the practices mentioned, mechanical pipefitting aids are required; eating, drinking, smoking, and storage of food are not permitted in the laboratory, and laboratory garments are required. Containment equipment is required to isolate operations that produce a considerable aerosol.

The principal item of containment equipment is the biological safety cabinet. This is an open-front cabinet with an inward airflow from the laboratory room of at least 75 linear feet per minute. The cabinet serves primarily to protect the operator from aerosols that may be created by the activities performed within the cabinet; it also serves to prevent the release of airborne contaminants to the environment. The air, which is exhausted from these cabinets, is either filtered by high efficiency, particulate air filters or incinerated. The high efficiency, particulate air filter is a filter capable of removing greater than 99.997 percent of all microorganisms that may be in the exhaust air.

At the P3 level, even more stringent laboratory practices are required in addition to those mentioned before. For example, long sleeve, solid front or wraparound surgical gowns are required to be worn by persons in the laboratory; protective gloves are worn when handling the research materials; hands are washed immediately following the removal of the gloves; only persons whose entry into the laboratory is required on the basis of program or support needs can be authorized to enter the laboratory; and vacuum systems are protected by filters and disinfectant traps. In addition, all operations which may produce aerosols must be confined to containment equipment.

The requirement for the use of containment is most important. Analysis of comprehensive surveys of laboratory-acquired infections demonstrates that fewer than 20 percent of known infections can be attributed to a documented accidental exposure. The knowledge that most microbiological practices create aerosols suggests that inhalation of undetected aerosols may contribute significantly to the potential of occupational illness among laboratory workers. For this reason, agents that have been assessed to be of moderate potential hazard are to be handled only in containment equipment.

The P3 laboratory is also equipped with certain facility safeguards. These include double-doored entryways which facilitate the control of access to the laboratory; controlled airflow where air moves in the direction of greatest potential hazard; discharge of general exhaust from the laboratory to the outdoors and its dispersal to clear occupied buildings and air intakes; and preparation of the surfaces of walls, floors, bench tops, and ceilings so that they are easily cleanable and so that housekeeping and space decontamination are facilitated.

The level of protection provided by the P3 laboratory is appropriate for the safe conduct of research involving agents of such diseases of man as tuberculosis, brucellosis, tularemia, Q fever, and rabies.

Physical containment providing the greatest safeguards for reducing the potential for accidental release of microorganisms are used at the P4 level. All research operations involving recombinant DNA materials are confined to class III biological safety cabinets. These

cabinets are physical enclosures which are gastight. Operations are performed through gloves which are attached to the cabinet.

The cabinets are maintained under negative air pressure and the exhaust air from the cabinets is either filtered through two sets of high-efficiency particulate air filters or filtered once and incinerated. Under ordinary circumstances of operation they provide an impenetrable barrier between the inside of the cabinet and the laboratory equipment.

Materials to be removed from the class III cabinets are either sterilized in an autoclave attached to the cabinets or they are placed into nonbreakable sealed containers which are then removed from the cabinet through a chemical decontamination tank or a fumigation chamber.

The class III biological safety cabinets are located in a facility that provides secondary safeguards which are designed to further reduce the potential for escape of micro-organisms to the environment. The facility is either a separate building or it is a controlled area, within a building which is completely isolated from all other areas of the building. Access to the facility is under strict control.

The secondary safeguards of the facility include:

Monolithic walls, floors and ceilings in which all penetrations such as for air ducts, electrical conduits, and utility pipes are sealed to assure the physical isolation of the work area and to facilitate housekeeping and space decontamination;

Air locks through which supplies and materials can be brought safely into the facility;

A contiguous clothing change and shower rooms through which personnel enter into and exit from the facility;

Double-door autoclaves to sterilize and safely remove wastes and other materials from the facility;

A biowaste treatment system to sterilize liquid effluents from the facility;

A separate ventilation system which maintains negative air pressures and directional air flow within the facility; and

A treatment system to decontaminate the exhaust air from the facility before this air is dispersed to the atmosphere.

I wish to emphasize that these secondary safeguards are not the primary means of control. For example, liquid and solid waste material generated within the class III cabinets must be sterilized before they are removed from the cabinets. These materials are then sterilized once again by facility safeguards such as the double-doored autoclave or the biowaste treatment plant before they are removed from the P4 facility.

In addition, all equipment and material to be removed from the laboratory environment, such as protective clothing, data sheets, and general glassware, must be sterilized before they are removed from the P4 facility.

Personnel who are authorized to enter the P4 facility remove all street clothing in a change room area and dress in complete laboratory clothing, including undergarments, pants and shirts or jumpsuits, shoes, head cover and gloves. This clothing is removed and showers are taken before personnel are allowed to leave the facility.

I would now like to direct your attention toward the value of these physical containment safeguards.

It is difficult to assess the value of secondary facility safeguards in providing protection to persons outside of the laboratory and the general environment. Most research involving human pathogens has been conducted using primary safeguards consistent with P1 and P2 descriptions. Until the last two decades, few secondary safeguards were employed. Laboratory exposures do occur under these conditions and a number of laboratory-acquired infections have resulted from such exposures.

In some instances, multiple infections have been reported in a single facility presumably resulting from a common source of infectious material. Nevertheless, the use of pathogens under conditions comparable to P1 and P2 has not resulted in infections among the general public. There have been a few reported infections—less than 1 percent of all recorded laboratory-acquired infections—among persons visiting a laboratory facility or who had a direct association with a laboratory worker having a laboratory-acquired illness.

This experience led Dr. Wedum to conclude that—and I quote—"As far as biohazard outside the building is concerned, most secondary barriers are more for reasons of public relations than for anything else, except for pilot plants or other large-volume production, experimental aerosols, use of tick or insect vectors, and agents capable of spread to the animal or plant food supply. This view assumes that known infectious liquids, solids, animals, and animal wastes are decontaminated before disposal, as has long been standard practice in all microbiological laboratories."

The use of secondary facility safeguards, as is required for P3 and P4 recombinant DNA experiments, will make the likelihood of potential hazard to the public and general environment even more remote.

The first line of defense for protecting the laboratory worker, persons outside the laboratory, and the general environment is provided by standard practices and primary containment equipment. An examination of the record of laboratory-acquired infections at Fort Detrick provides a basis for demonstrating the value of these primary safeguards.

From 1943 through 1945, most research with human pathogens at Fort Detrick was conducted on the open bench. This condition was comparable to what is now described as P1. The frequency of laboratory-acquired infections during this period was approximately seven infections per 100 person-years worked.

Primary containment equipment was not used extensively at Fort Detrick until after 1950, when this equipment became commercially available. During the period 1950 through 1960, this equipment was assigned on a risk-priority basis to programs in which considerable aerosol exposure were likely to occur. Records from 1954 through 1958, when this equipment was selectively used, indicate that the infection rate was approximately two infections per 100 person-years worked. This condition was comparable to what is now described as P2.

Most research involving high-risk human pathogens at Fort Detrick after 1960 was conducted in open-fronted biological safety cabinets. This period was comparable to our current P3 descriptions.

The infection rate during one period after 1960 was approximately 0.4 infections per 100 person-years worked.

Chairman THORNTON. Dr. Barkley, I hesitate to interrupt, but I think members of the committee have now had an opportunity to read through most of the balance of this statement, and I wonder if you might summarize the high points of the remaining portion of this statement in order that we may accommodate the time of the other witnesses and give us an opportunity to call for questions and answers. If it's posible for you to summarize it, I would appreciate that, sir.

Dr. BARKLEY. Certainly.

Chairman THORNTON. Without objection, your statement in full will be made a part of the record.

Dr. BARKLEY. Thank you.

[The remainder of Dr. Barkley's statement follows:]

The safeguards described for P4 level physical containment are of recent development and have only been required for limited operations involving highly hazardous human pathogens. This combination of safeguards was used continuously in only one research facility at Fort Detrick during a ten year period ending in December of 1969. Within this facility, 55 employees, of whom 45 were daily involved in research, carried a weekly work load that commonly included the intracerebral inoculation of 6,000 to 8,000 mice and the whole-body exposure to microbial aerosols of 200 to 300 guinea pigs and 20 to 30 monkeys with all the associated preliminary and subsequent procedures. Agents capable of causing serious disease in man were used. The safety record within this facility was excellent. There was only one laboratory-acquired infection over this ten year period.

An absolute correlation between the reduction in rate of laboratory-acquired infections and the use of primary safeguards, however, is difficult to establish from the Fort Detrick experience. There were a variety of etiologic agents employed in research at Fort Detrick during this period. The use of biological safety cabinets was dependent on their availabiiity and assignment. Also, the introduction of effective vaccines for some of the agents that were handled, such as anthrax in 1954, tularemia in 1959, and Venezuelan encephalitis in 1962, may have influenced this experience. I believe, however, that the reduction in rate of laboratory-acquired infections at Fort Detrick was due primarily to the availability and use of primary safeguards.

The one infection which occurred under comparable P4 conditions at Fort Detrick was caused by a needle puncture through the attached glove of a Class III biological safety cabinet. This infection demonstrates that even under the most sophisticated containment conditions, accidents can occur. Indeed, the success of physical containment safeguards at all levels is dependent on the attitude, training, diligence and proficiency of the laboratory worker. This is why the NIH Guidelines require that "all personnel directly or indirectly involved in experiments on recombinant DNA's must receive adequate instruction."

In addition to training in the use of physical containment safeguards and standard microbiological techniques, instruction in the biology of the organisms used in the experiments is required so that the potential biohazards can be understood and appreciated. A laboratory worker who is aware of the potential hazards of the research and is proficient in the use of safeguards is less likely to be injured or to cause harm to associates, the general public or the environment.

I am aware of 25 government, 4 university and 5 industrial facilities which currently possess most of the primary and secondary safeguards required of P4 facilities. Most of these facilities were constructed between 1950 and 1970 for the purpose of supporting research involving high risk human or animal pathogens. These facilities, if used for P4 recombinant DNA research would require extensive rehabilitation. A few facilities have been recently constructed to provide a capability for containing newly isolated microorganisms but only two of these are currently being operated under conditions comparable to P4. Indeed, not all of these facilities are being employed for research with microbiological agents.

At the present time NIH is considering the rehabilitation of four facilities to support recombinant DNA research. Two facilities are located at the Frederick Cancer Research Center and two facilities are located on the NIH campus in Bethesda.

Dr. BARKLEY. I would like to summarize by saying that we have developed in this country a capability which allows us to safely handle the most hazardous micro-organisms known to man. This capability does exist in a number of facilities and institutions in this country.

Our experience to date has demonstrated that work with known human pathogens can be conducted in a manner which does not endanger the general public.

I would like to emphasize, however, that the success of physical containment measures is dependent on the attitude, training, diligence, and proficiency of the laboratory worker in implementing these safeguards and understanding the potential risks associated with the work.

With this understanding, combined with the availability of appropriate physical containment safeguards, I think we do possess the capability to protect the public from the potential hazards that may be associated with recombinant DNA research.

Chairman THORNTON. You point out in the balance of your prepared testimony that at Fort Detrick there was one accident which occurred when a glove was penetrated by a needle puncture, apparently. That points up the importance of biological containment which can be employed in connection with physical containment.

I want to thank you very much, Dr. Barkley, for your testimony and for your summarizing your prepared and excellent statement. Our next witness will deal with the question of biological containment.

Dr. Curtiss is professor in the department of microbiology at the University of Alabama Medical Center, Birmingham, Ala. Dr. Curtiss, we do have your prepared statement before us. Without objection it will be made a part of the record.

I would like to ask you to proceed to highlight that statement as you may see fit.

[A biographical sketch of Dr. Curtiss follows:]

ROY CURTISS III

Roy Curtiss III; place of birth: New York, N.Y.; birthdate: May 27, 1934; age: 42; education: Cornell University, Ithaca, N.Y., Agriculture, B.S. 1956; University of Chicago, Chicago, Ill., Microbiology, Ph.D. 1962.

Present position: Professor of Microbiology; Senior Scientist, Cancer Research and Training Center; Senior Scientist, Institute of Dental Research, University of Alabama in Birmingham.

Research interests: Microbial and molecular genetics (1956–present). A principal research activity during the past 17 years has concerned the mechanism of conjugational gene transfer in *Escherichia coli* K–12. In 1969 this was extended to include the machinisms of replication, expression and transmission of plasmids conferring antibiotic resistance and other traits contributing to bacterial virulence. Studies on the genetics and biochemical basis of pathogenicity of oral Streptococci commenced in 1973 and a principal activity since 1975 has been the design, construction and testing of safer strains of *E. coli* K–12 for recombinant DNA research. This latter endeavor has been intermeshed with studies to elucidate and evaluate the likelihood of survival and transmission of recombinant DNA molecules contained on non-conjugative plasmid cloning vectors. There have been 46 publications resulting from this research. No research utilizing recombinant DNA molecule technologies is currently underway, but such experiments are likely to commence later in 1977.

Honors: Member, NIH Recombinant DNA Molecule Advisory Committee (1974–Present). Member, International Council of Scientific Unions Ad Hoc Committee on Recombinant DNA (1976). Member, NSF Genetic Biology Advisory Panel (1975–Present). Member, Board of Directors, Council for the Advancement of Scientific Writing, Inc. (1975–Present). Editorial Board Member (1966–70) and Editor (1970–1976) of *Journal of Bacteriology*. Lecturer, American Foundation for Microbiology (1969–70). Vice President (1967–68) and President (1968–69), Kentucky and Tennessee Branch, American Society for Microbiology. Recipient of P. R. Edwards Award of the Southeastern Branch of the American Society for Microbiology, 1975. Parliamentarian, American Society for Microbiology (1970–75). Member, Membership Committee, American Society for Microbiology (1971–Present). Chairman, Nominating Committee, Division of Genetics and Molecular Biology, American Society for Microbiology (1973). Member, Council Policy Committee, American Society for Microbiology (1977–Present). Councilor, Southeastern Branch, American Society for Microbiology (1976–77). Fellow, American Academy of Microbiology (1974–Present). Member, Genetics Society of America, Society for General Microbiology, American Society for Microbiology, New York Academy of Sciences, American Association for the Advancement of Science and Sigma Xi, Honorary Member, Asociacion Chilena de Microbiologia (1973). Visiting Professor, Instituto Venezolano de Investigaciones Cientificas, 1969; University of Puerto Rico, 1972; Universidad Catolica de Chile, 1973.

Consultantships: Serve on advisory committees of the National Institutes of Health and National Science Foundation.

Patents pending: Research Corporation and the University of Alabama in Birmingham have filed a patent in the United States, Great Britain, West Germany and Japan entitled "Modified Microorganisms and Method of Preparing and Using Same" which is based on the biological containment systems designed and developed in the course of research supported by the National Institutes of Health and the National Science Foundation.

STATEMENT OF DR. ROY CURTISS III, PROFESSOR, DEPARTMENT OF MICROBIOLOGY, UNIVERSITY OF ALABAMA MEDICAL CENTER

Dr. CURTISS. Thank you.

Mr. Chairman, ladies and gentlemen, I think Dr. Barkley has described physical containment, which is a rather traditional although still developing means, to protect the laboratory investigator, and equally important, individuals outside of the laboratory environment.

Recombinant DNA research, because of its very nature and because the technology was developed by molecular biologists and geneticists, lends itself to a new type of containment termed biological containment. Biological containment refers to the use of the viral and plasmid cloning vectors described by Dr. Singer that have been genetically altered so as to make their perpetuation dependent upon a particular host strain, very often a bacterium which has also been genetically manipulated so that if it should escape the laboratory environment, it would have a very small chance of survival in nature or of transmitting, by known mechanisms of gene exchange among micro-organisms, the recombinant DNA to other organisms encountered in nature.

Recombinant DNA research technology was discovered during basic studies in molecular genetics of the bacterium *Escherichia coli*, wherein investigators were trying to understand mechanisms of drug resistance conferred by plasmids—some of which are now used as cloning vectors—and also mechanisms that preclude or minimize gene transfer in nature.

Because recombinant DNA experiments were done with *E. coli*, which has been the workhorse of molecular biology for years and

years, there was great concern expressed by some individuals both within and outside the scientific community. This concern was because *Escherichia coli*, or *E. coli* for short, is a normal inhabitant in the intestinal tract of all warmblooded animals, is occasionally associated with causation of diseases like urinary tract infections and is also rather ubiquitous in our environment, very much because of the pollution due to the human species and our societal habits.

However, the strain of *E. coli* that is used for this research is a strain that's called *Escherichia coli* K–12, and it became a popular research organism in the forties due to basic studies by Lederberg and Tatum. A lot of people think that *E. coli* K–12 is just like all other *E. coli*'s, and that's about like saying that all automobiles are Mercedes-Benz. There are *E. coli*'s and there are other *E. coli*'s. And *E. coli* K–12 is an attenuated strain: It's been in the laboratory environment since 1922.

During many studies, it's been shown that when *E. coli* K–12 is fed to a diversity of normal organisms, whether they be mice or humans, the *E. coli* passes right through without ever establishing itself in the intestinal tract. It is known, however, that *E. coli* K–12 can survive passage through the intestinal tract and actually can stay there longer if the person is debilitated in some way by malnourishment or is being given antibiotic therapy.

Some of the plasmid and virus vectors that Dr. Singer talked about are quite well contained to *E. coli* K–12. There are really two types of plasmids, and I need to distinguish between them: One is called a conjugative and the other a nonconjugative plasmid.

Bacteria can engage in sex just like most other organisms, although they do so very rarely. And some plasmids have the ability of promoting a cell-mediated gene transfer called conjugation, and these are called conjugative plasmids. On the other hand, those plasmids that can't do this are called nonconjugative plasmids, and these are the types of plasmids that are used in recombinant DNA research so as to minimize the likelihood that a piece of cloned DNA on such a plasmid would be transmitted to some other organism encountered in nature.

The virus vectors used are also ones that grow on *E. coli* K–12 and most strains of *E. coli* encountered in nature are resistant to that virus.

So, both nonconjugative plasmid and bacteriophage cloning vectors, are quite well contained. Consequently, *E. coli* K–12 with these two types of vectors is considered to afford a moderate level of biological containment. It is thus usable for those experiments that have low or minimal risk, according to the NIH guidelines.

However, there are other experiments that are riskier, or at least we think they might be riskier. Nobody really knows. And these require different types of *E. coli* host-vector systems that are designated EK2—the "E" for Escherichia and the "K" for K–12—and EK3.

The EK2 host-vector system is one in which the probability of survival of the recombinant DNA by survival of the bacterium or the transmission of the vector to some other organism is reduced 100-million times over what one would observe with standard *E. coli* K–12 strains.

Since March of 1975, our laboratory has been working to design fail-safe strains of *E. coli* K–12 for this research, and we have used a variety of approaches to do this.

One of them was to design bacteria that, if they escaped the laboratory environment, would be unable to synthesize their cell wall and their DNA which would lead to their early death and demise and the destruction of the recombinant DNA.

We have introduced other genetic defects, called mutations, that make these strains very sensitive to environmentally-encountered agents, such as bile, which is secreted into the intestine by all warm-blooded animals. Thus, the organisms cannot survive passage through the intestinal tract.

We have made them sensitive to ultraviolet light so they would be very sensitive to sunlight.

We have made them sensitive to detergents, chemicals, carcinogens, mutagens, etc., a variety of pollutants that might likely be encountered in sewage, rivers, and any other polluted environments.

And, lastly, we have introduced mutations that would minimize the likelihood that these bacteria could engage in any means by which the recombinant DNA could be transmitted to other bacteria in nature.

The EK3 level of biological containment refers to those systems that have been independently tested by a number of people to evaluate survival of the strains in and on humans, in sewage and during sewage treatment, and during various types of laboratory manipulations that might be done and during accidents.

Other groups at NIH, the University of Wisconsin, and at MIT, have developed improved virus vectors for research with *E. coli* K–12 that are essentially unable to establish any type of symbiotic relationship with the bacterial host and which lead to the complete lysis and destruction of host cells. These virus vectors also have mutations so that they can only propagate on a given host strain of *E. coli* K–12 but not on other strains that might be encountered in nature.

A number of these *E. coli* K–12 strains with virus and plasmid vectors have been approved by the NIH as EK2 systems for use in experiments with a moderate to somewhat high potential biohazard. Tests are currently underway to determine whether these host vectors meet the EK3 criteria of biological containments.

I should say, in closing, that the combination of physical and biological containment affords a great margin of safety in recombinant DNA research. From my own point of view I can think of no experiment that is allowed under the guidelines which, when these methods are adhered to, poses any hazard whatsoever.

The limitation to this conclusion, however, in an attribute of the human species. Humans do experiments, and they do make mistakes. Thus I think that an important aspect to further minimizing any potential biohazard of recombinant DNA research has to lie with appropriate training of individuals and in taking steps to minimize human error.

Thank you.

[The prepared statement of Dr. Roy Curtiss III is as follows:]

BIOLOGICAL CONTAINMENT IN RECOMBINANT DNA RESEARCH
Testimony Presented by Roy Curtiss III
Before the Subcommittee on Science, Research and Technology
March 29, 1977

Mr. Chairman, ladies and gentlemen, you have just heard Dr. Emmett Barkley describe the types of physical containment facilities, equipment and procedures that have been traditionally used in research with biohazardous materials so as to protect the scientific investigator as well as other members of society outside the laboratory environment. Recombinant DNA research, however, by its very nature lends itself to a new type of containment that further reduces the likelihood of harm should an organism containing recombinant DNA escape the laboratory environment. This new type of containment is termed "biological containment" and refers to the use of viral and plasmid cloning vectors that have been genetically altered so as to make their perpetuation dependent upon propagating host strains that have also been genetically altered to make them less able to survive or transmit recombinant DNA to other microorganisms outside of the carefully controlled laboratory environment.

Recombinant DNA molecule research grew out of basic studies on the mechanisms of antibiotic resistance specified by circular extrachromosomal DNA elements called plasmids that are ubiquitous among bacteria in nature and the mechanism of a process termed "restriction", which acts as a barrier to gene transfer between bacteria in nature. These classic studies were performed using the bacterium Escherichia coli, which has been since 1940 the workhorse for molecular biology research. Indeed, we know more about the physiology, genetics and cell biology of E. coli than about any other living organism. Concern about the potential biohazards of recombinant DNA research derives from the fact that strains of E. coli are inhabitants of the intestinal tracts of all warm-blooded animals, are "abnormal" inhabitants of our streams, rivers, lakes, estuarine waters, etc. and of soils in urban and agricultural areas and cause the majority of urinary tract infections and are often associated with infections of patients whose normal host defense mechanisms are compromised by surgery, transplantation or diseases such as cancer. Not all strains of E. coli are alike, however, and this species contains a diversity of types as varied as found in the species Gallus gallus (chickens) or Canis familiaris (domestic dogs) with which we are more familiar. The only strain of E. coli permitted for use in recombinant DNA research is a strain designated K-12 which became popular for genetic and molecular biology research in the mid-1940's due to the classic studies of Drs. Joshua Lederberg and Edward L. Tatum on the mechanism of gene transfer in bacteria. E. coli K-12 was isolated from a human patient at Stanford Medical Center in 1922 and has been cultivated in the laboratory since that time. During its laboratory sojourn, it has undergone genetic changes so that it has become better adapted, if not semi-addicted, to the foods and environments provided in the microbiology laboratory. In so doing, E. coli K-12 has become quite dissimilar from E. coli strains that normally inhabit (i.e., colonize) the lower intestine of warm-blooded animals. Thus, in numerous experiments in which E. coli K-12 has been fed to healthy, well-nourished mice, rats, chickens, pigs, calves and humans, it has not been possible to demonstrate colonization of the intestinal tract. It is known, however, that E. coli K-12 survives passage through the intestinal tract and is able to colonize animal species that have been fasted for a day or two before feeding and also in human volunteers who have been treated with antibiotics to eliminate the normal intestinal flora. I should

add that nothing is known about the ability of E. coli K-12 in comparison to other E. coli strains to survive in sewage and during sewage treatment.

The cloning vectors used for recombinant DNA research in conjunction with host strains of E. coli K-12 include derivatives of the bacterial virus lambda and non-conjugative plasmids. Non-conjugative plasmids are those that are incapable of promoting cell-mediated gene transfer by the process of conjugation. Bacteriophage lambda is sensitive to dessication, stomach acidity and detergents and less than 1% of wild-type E. coli strains encountered in nature are able to be infected with it. Thus recombinant DNA cloned on lambda vectors, even if encased in an infectious virus particle, is not likely to survive and be perpetuated in nature. The non-conjugative plasmid cloning vectors only duplicate in a living bacterial cell and thus the survival of recombinant DNA contained on them is dependent upon the survival of the bacterial host cell and/or the ability of the recombinant plasmid to be transmitted to some other more robust microorganism encountered in nature. Transmission of recombinant DNA contained on non-conjugative plasmids could be by either of two means. In the first, the cell could be infected by a suitable bacterial virus that could pick up the recombinant plasmid and transmit it to some other microorganism by a process termed "transduction". Although little quantitative information is available about the ecology of bacterial viruses that could do this, our knowledge from laboratory experiments leads me to believe that this would be an extremely rare event. The second means of transmission would be by the process of bacterial conjugation. This would require that the host cell containing the recombinant non-conjugative plasmid first engage in a conjugational act with a donor strain possessing another type of plasmid termed a "conjugative plasmid" that promotes DNA transfer by a cell-cell-mediated process. Upon acquisition of a conjugative plasmid, the host cell containing the recombinant plasmid vector would then have to engage in conjugation with a third bacterial cell in order to pass on the recombinant plasmid. Based on rather extensive studies in our own laboratory, this series of events is also deemed to be extremely rare but would be more likely to occur at body temperature than at the lower temperatures found in sewers, sewage treatment plants, rivers, soil, etc.

Because of these properties of E. coli K-12 and of the bacteriophage lambda and non-conjugative plasmid cloning vectors, these systems are considered to provide a moderate level of biological containment. Such host-vector systems are designated EK1 - E for Escherichia and K for the K in K-12. These systems are permitted to be used for recombinant DNA molecule experiments possessing no or minimal potential biohazard.

For many recombinant DNA molecule experiments in which the potential biohazard has been estimated to be higher, there are stipulations in the NIH Guidelines for Recombinant DNA Molecule Research for higher levels of biological containment than afforded by the EK1 host-vector systems. These higher levels of biological containment for the E. coli K-12 systems are referred to as EK2 and EK3. An EK2 host-vector system is one in which the genetic modifications of the host and/or vector are shown in a diversity of laboratory tests to reduce the survival of a recombinant DNA molecule to less than one in one-hundred million. An EK3 host-vector system is an EK2 system that has been independently tested and its properties confirmed in animal and human feeding experiments, in sewage and during sewage treatment and during simulated laboratory manipulations including accidents.

Since March of 1975, our own laboratory group has endeavored to design, construct and test safer, more useful host strains of E. coli K-12 for recombinant DNA research. We have used three approaches to reduce the probability for survival of a recombinant DNA molecule should the organism containing it inadvertently escape the laboratory environment. First, we introduced a constellation of genetic defects (i.e., mutations) that resulted in the destruction of the bacterial cell and its genetic information if it should attempt to grow outside its carefully controlled testtube environment. Second, we introduced another constellation of mutations that caused the strain to be extremely sensitive to various environmentally encountered substances or physical environments that would cause cell death independent of the attempts of the organism to grow. Third, we introduced a constellation of mutations that reduced the likelihood of transmission of recombinant DNA to other robust microorganisms that could be encountered in nature. Wherever possible, we used mutations in which all or part of the gene specifying the function was removed so that the function could not be restored by reverse mutation. In other instances, we used two separate mutations to eliminate the same function. In January of 1976, our laboratory completed the construction of an E. coli K-12 host strain that would be useful for recombinant DNA molecule research in conjunction with non-conjugative plasmid cloning vectors and which possessed the safety features cited above. This strain, which contains 15 separate genetic defects, was designated χ1776 in celebration of the bicentennial. Bacteria have a rigid cell wall which is composed of unique building blocks that are found only in bacteria and not in higher organisms. χ1776 is unable to synthesize one of these building blocks and in its absence the cell wall splits apart and the cell lyses. χ1776 is also unable to synthesize its DNA unless supplied with one of the essential building blocks of DNA, a substance termed thymidine. In the absence of thymidine, χ1776 rapidly undergoes death with the destruction of its genetic information and displays a total inability to transmit that information to other microorganisms. χ1776, unlike normal E. coli strains, is extremely sensitive to bile, which is secreted into the small intestine, and consequently this strain has never been observed to survive passage through the intestinal tracts of rats except when the animals had been treated with antibiotics the day before feeding of the strain. χ1776 is extremely sensitive to detergents and thus less likely than normal E. coli strains to survive in sewage and during sewage treatment, and is also extremely sensitive to many chemicals, carcinogens, antibiotics and other substances that might likely be encountered in polluted rivers, streams, etc. It is unable to repair damage to its genetic information inflicted by ultraviolet light and is thus much more sensitive to sunlight than normal strains of E. coli. Finally, χ1776's cell wall has been altered by numerous genetic mutations so as to very much reduce its ability to transmit recombinant DNA to other organisms by either transduction or conjugation. Since χ1776 can lyse in the intestinal tract, numerous individuals have wondered whether the released DNA might be taken up by other microorganisms by a process termed transformation even though this process is not known to normally occur in enteric bacteria. We have recently demonstrated that the intestinal tract of both conventional and germ-free rats has a very high content of enzymes that very rapidly degrade DNA, thus further minimizing the likelihood of this route of escape of recombinant DNA. This conclusion, of course, is based on the reasonable assumption that the intestinal tract of humans is similar in this respect to that of rats. Drs. Herbert Boyer of the University of California at San Francisco and Donald Helinski of the University of California at San Diego and their colleagues have constructed a number of improved non-conjugative plasmid cloning vectors that are less likely

to be transmitted from χ1776 or to have a selective advantage in nature, thus adding another level of safety improvement over EK1 host-vector systems. It should be noted, however, that no one has yet discovered appropriate mutations to introduce into non-conjugative plasmid cloning vectors that would make their replication solely dependent upon the propagating host strain. χ1776, in conjunction with several of these plasmid cloning vectors, was designated as meeting the EK2 host-vector requirements by Dr. Donald Fredrickson, Director of NIH, in November of 1976.

Drs. Frederick Blattner of the University of Wisconsin at Madison, Philip Leder of the National Institutes of Health and Philip Sharp of the Massachusetts Institute of Technology and their colleagues have individually designed and constructed safer bacteriophage lambda vectors. These vectors have a diversity of genetic alterations that very much minimize their ability to establish a symbiotic relationship with the propagating bacterial host cell, thus causing lysis of all infected cells. They also possess mutations that make them dependent upon the propagating host for their replication. We have designed and constructed a bacterial host designated χ1953 or DP50 that has some but not all of the features of χ1776 for use with some of these lambda vectors. Some of these host-vector systems have already been approved as meeting the EK2 standards and others are pending approval.

χ1776 and a number of the other components of EK2 host-vector systems have been criticized by some members of the scientific community as not being sufficiently perfect and in not having been tested in human feeding experiments and during waste water collection and sewage treatment. It is certainly true that χ1776 and some of the vectors in EK2 systems are not perfect. For example, χ1776 survives almost as well as normal E. coli strains when suspended in pure water or when dried; and this potential for persistence is bothersome, even though we would not expect and indeed cannot experimentally measure any potential for transmission to other microorganisms of recombinant DNA contained in χ1776 under these conditions. It should be pointed out that the development of biological containment systems is in its infancy and that improvements are continually being made as new information is obtained. As for the safety tests not yet done, these are part of EK3 testing, which is just commencing.

In this commentary, I have not mentioned attempts to develop biological containment systems for recombinant DNA research using other bacterial hosts or the cells of higher organisms such as mammals, plants and insects. This is because the development of recombinant DNA methods in most of these systems is either yet to be discovered or in a very primitive stage of development. The general concepts and approaches used to achieve biological containment with E. coli K-12 host-vector systems are, however, applicable to these other systems. Although the NIH Guidelines for Recombinant DNA Molecule Research provide general principles for achieving biological containment with other systems, detailed specifics are not provided. These will have to be added as new information is learned and these other systems are developed. Thank you.

Chairman THORNTON. Thank you, Dr. Curtiss.

Many have remarked that one of the most immediate possible applications of DNA research might be in the agricultural or plant sciences. For that reason, we have invited a witness from the agricultural research community to testify today, Dr. Charles Lewis, who is a staff scientist with the Agricultural Research Service at Beltsville.

Dr. Lewis, we have received your prepared testimony, and without objection that prepared testimony will be made a part of the record. Wo would like to ask you now to proceed.

Dr. Curtiss, before recognizing Dr. Lewis, I do want to commend you on your very excellent summary of your written paper. Thank you.

Dr. Lewis.

[A biographical sketch of Dr. Lewis follows:]

Bibliography, Charles F. Lewis

Present title: Staff Scientist, Plant Genetics and Breeding, National Program Staff, Agricultural Research Service, USDA, Beltsville, Md. (July 1, 1972-Present).

Born in Blooming Grove, Texas, July 25, 1917; married Ruth Neeley in 1944; has 2 children.

Education:

B.S., Agronomy 1939, Texas A&M University, College Station, Texas
M.S., Genetics 1940, Texas A&M University, College Station, Texas
Ph.D., Genetics 1951, University of California

Work Record:

1958-1972 - Research Geneticist, Cotton and Cordage Fibers Research Branch, Crops Research Division, ARS, USDA, Beltsville, Maryland

1941-1958 - Agent (Agricultural Aid), joint employee of the Texas Agricultural Experiment Station and the Cotton & Cordage Fibers Research Branch, USDA, College Station, Texas

1941-1945 - Active duty, U.S. Navy (Present status, CDR, USNR, Ret.).

Honors and Awards:

USDA Distinguished Service Award, 1977
Genetics and Breeding Award, National Council of Commercial Plant Breeders, 1975
USDA Superior Service Honor Award, 1965
Cotton Genetics Research Award, 1965; given annually by commercial cotton breeders in U.S. in recognition of outstanding research accomplishments
Fellow, American Society of Agronomy, 1965
General Education Board, Natural Science Fellowship, University of California, 1948-49
Sigma Xi

Professional Affiliations:

American Society of Agronomy
Genetics Society of America
Associate Editor, Journal of Environmental Quality, 1973-1975
Chairman, Crop Registration Committee, CSSA, 1972-

Dr. Lewis is a recognized national and international authority on the genetics and breeding of cotton, and has made contributions through many publications and invitational papers. He has served as Executive Secretary of the National Plant Genetic Resources Board, established by the Secretary of Agriculture in 1975, and was the USDA representative to the Federal Interagency Committee on Recombinant DNA Research.

STATEMENT OF DR. CHARLES LEWIS, STAFF SCIENTIST, AGRICULTURAL RESEARCH SERVICE, BELTSVILLE

Dr. LEWIS. Thank you, Mr. Chairman.

The potential significance of recombinant DNA research for agriculture can be assessed better if it is placed in perspective with regard to genetic knowledge, to natural history, and agriculture.

I think it's important to read the definition of recombinant DNA as you find it in the guidelines. It's defined:

> As molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome.

This is what Dr. Singer demonstrated so clearly at the outset. It is important to realize that this refers to one way to recombine DNA's, and it is by no means the only way.

Agricultural scientists believe that recombinant DNA technology has great potential for the future, although it has had no impact on practical agriculture to date. Now, the science of genetics has been used in agriculture to improve the productivity and the quality of the plants and animals that provide food, fiber, forest products, nursery crops, and many other useful products.

Genetic improvement has accounted for a significant part of the great increase in agricultural production over the past 30 to 40 years. This advancing technology that recombinant DNA represents should lead in time to practical applications.

This technology represents a recent development based on an increasing understanding of the nature and the function of hereditary materials. Knowledge of heredity began I suppose with ancient people who observed that "like begets like." The understanding of heredity advanced with the discovery of Mendel's laws of dominance, independent assortment and segregation of characters.

This was followed by the discovery of threadlike structures in cells called chromosomes, and to the fact that the hereditary traits were located on the chromosomes. Later the chromosomes were found to be composed of deoxyribonucleic acid, DNA. And, finally, as you've heard this morning, the molecular structure of DNA was discovered and the genetic code was broken.

Molecular biologists, working primarily with micro-organisms, learned how to artificially manipulate DNA in cell-free systems to produce the recombinant DNA molecules.

In discussing this with people who are not geneticists or molecular biologists, I have found it useful to use analogies. A DNA molecule might be thought of as a twisted ladder where the two sides are composed of phosphate and sugar groups, and the connecting rungs being pairs of bases connected by hydrogen bonds. There are only four bases and only two pairings—adenine with thymine (A–T) and quanine with cytosine (G–C). There's one analogy.

Another analogy is useful in explaining the code. The English alphabet has 26 letters. Words are formed by putting the letters together in linear combinations. Sentences are formed by arranging words in linear sequences. You can write the Bible, the Constitution of the United States, a legislation, Shakespeare's works, or the daily news-

paper, or anything else the mind can express. So it is, in a way, with the genetic code of life. There are only four letters—A, T, G, and C—and all the words are three-letter words. By arranging the words, or these genetic codes, in linear sequence, this imparts to all living things their genetic potential. The infinite ways the code may be constructed give to the four bases the capability of producing all forms of life, from viruses to humans.

One way to place recombinant DNA technology into natural history and agricultural perspective is to utilize an outline, and I'll not read this word-for-word, but summarize it, Mr. Chairman.

Chairman THORNTON. Thank you very much.

Dr. LEWIS. But this outline is concerned with the recombination of DNA in general, not just that narrowly defined as recombinant DNA.

First, consider natural recombination. In the history of the Earth DNA is as old as life, and DNA has been recombining since the beginning. Modification through descent by variation and natural selection formed the array of genetic diversity among and within species.

Let's next consider the human-directed recombination or human intrusion into the natural order of things. We might think of it as being the cellular and sexual approach, as opposed to the cell-free system you've heard described.

Selection was practiced by early agriculturalists. They doubtless selected for their breeding stocks those plants and animals that produced the best quality products for them.

Modern plant breeders still practice selection, and it remains a powerful way to shift the genetic composition of a whole population. Now, the organism selected is not changed genetically. It's allowed to reproduce, and all the rest of them in the population which it is drawn from are denied that privilege.

Today plant and animal scientists utilize hybridization to develop populations with a wide array of segregating characteristics representing almost infinite recombinations of traits from the different parental stocks. By selection and evaluation and repeating the process over and over, plants and animals can be bred with the genetic composition—or arrangement of DNA, if you please—to achieve many desirable objectives.

This sexual, cellular approach has been used to make great improvements in the productivity and quality of agricultural plants and animals. This approach will continue to be an important one in agriculture.

Now, in your prepared statement I have listed several ways that DNA recombines occur naturally, and we won't go into detail unless you want——

Chairman THORNTON. We do appreciate having that list. It is a very comprehensive list.

Dr. LEWIS. But it includes independent assortment, crossing-over, mutation, ploidy, interspecific and intergeneric gene transfer, cytological abnormalities, somatic cell fusion, cell culture and selection, and tissue culture, transduction, and transformation.

We finally come, as far as the outline is concerned, to the cell-free asexual approach, which we're calling recombinant DNA.

Chairman THORNTON. In that regard, I may inquire, at the bottom of page 6, just before you get to the cell-free type of recombination,

you mention transduction and transformation. Each of these categories it seems to me is very closely related at least to the use of the technology which has been previously described here today: using a filterable agent as a bacteriophage; or transformation of hereditary material from a donor bacterium to a recipient bacterium by plasmids.

I would assume that that does fit within the technology of recombining which has been described to us today. Does it not?

Dr. LEWIS. It's getting on the borderline, but——

Chairman THORNTON. Some of these——

Dr. LEWIS. Some of these things may not have been combined with anything, such as she described.

Chairman THORNTON. OK. But these are borderline incidences which are asexual, but not cell-free, recombinant DNA technology? Is that correct?

Dr. LEWIS. Yes.

Chairman THORNTON. Thank you.

Dr. LEWIS. Now, with the possible exception of the cell-free, asexual technique, nature employs all the techniques which I have listed under human-directed recombination. The differences are that humans can speed up the process, and humans can direct the efforts toward goals of advantage to people.

Agricultural scientists recognize that recombinant DNA technology expands the range of life over which DNA can be manipulated. This allows DNA's to be recombined among organisms which do not ordinarily exchange DNA. As the science advances, it should increase the precision with which DNA can be manipulated.

Now, objectives for agricultural research are set primarily by the needs of people and by the problems faced in the production, harvesting, storing, transporting, processing, and marketing of agricultural products. Sometimes objectives are set as new scientific information reveals new opportunities which did not occur to anybody before the discoveries were made.

Recombinant DNA technology will not make any major changes in the objectives of agricultural research. It offers another approach to achieving these objectives, and it may allow objectives to be reached which could not be achieved otherwise and it may make others easier to achieve.

Some possible uses of recombinant DNA technology in agriculture are under preliminary investigations, but most of them are in discussion or speculative stages.

Nitrogen fixation is mainly achieved by an interrelationship of certain bacteria and legumes. In view of the energy crisis and the use of fossil fuels to make nitrogen fertilizer, it would be highly desirable if bacteria could be found to fix nitrogen with plants other than legumes. Nitrogen fixing bacteria in grasses have been reported. Now, it's not too farfetched to imagine that recombinant DNA technology might be used to enhance this ability.

Biological control of pests is needed in order to reduce the dependence on chemical pesticides. For example, there is *Bacillus popilliae*, which attacks Japanese beetles and certain other white grubs. The difficulty is it cannot be readily grown in an artificial culture. Another bacteria, *Bacillus thuringiensis*, can be readily mass produced in culture, but it won't attack the pests. Recombinant DNA technol-

ogy might be used to develop bacteria that are easy to culture and able to attack the grubs and the other pests.

Ruminant animals utilize bacteria in the digestion of feed and some of them are very inefficient digesters. Such bacteria might be modified to more efficiently utilize forage, roughages, and to digest feeds not now commonly fed to animals.

Photosynthesis is the process whereby green plants use the energy of the Sun to convert carbon dioxide and water into carbohydrates and oxygen. Life on Earth depends on this process. Now, some plants are more efficient than others, and possibly DNA could be modified to improve photosynthesis efficiency.

Scientists are learning of the internal biochemistry of cells to the point where specific enzymes for the formation of proteins are known. It might eventually be possible, as has been pointed out already, to synthesize genes to produce a desired biochemical function and insert them into cells through DNA technology.

Agricultural scientists intend to investigate the possibility of inserting DNA into the genomes of higher plants and animals with plasmids as is done with bacteria, and perhaps put DNA into bacteria to study the functions.

In conclusion, I think we'd like to say that recombinant DNA technology in agriculture would be viewed as a supplement to, not a replacement of, our many traditional approaches. Agricultural scientists have made good use of the increasing understanding of the nature and function of hereditary materials.

Recombinant DNA technology represents a major new development, and we would try to find practical applications for it also.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Charles Lewis follows:]

TESTIMONY BEFORE THE SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY OF THE COMMITTEE ON SCIENCE AND TECHNOLOGY

By

Dr. Charles F. Lewis
National Program Staff
Agricultural Research Service
United States Department of Agriculture

MARCH 29, 1977

The potential significance of recombinant DNA research for agriculture can be assessed better if it is placed into perspective with regard to genetic knowledge, to natural history, and agriculture. Recombinant DNA molecules have been defined in the National Institutes of Health (NIH) Guidelines "as molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome." At the outset, it is important to realize that this refers to one way to recombine DNAs; it is by no means the only way.

Agricultural science believes recombinant DNA technology has great potential for the future although it has had no impact on practical agriculture to date. The science of genetics has been used in agriculture to improve the productivity and quality of plants and animals that provide food, fiber, forest, nursery, and other useful products. Genetic improvement has accounted for a significant part of the great increases in agricultural production over the past 30 to 40 years. The advancing technology that recombinant DNA represents should lead to significant practical applications.

The recombinant DNA technology represents a recent development based on an increasing understanding of the nature and function of hereditary materials. Knowledge of heredity began with ancient people who observed that "like begets like." The understanding of heredity advanced with the discovery of Mendel's laws of dominance, independent assortment and segregation of characters. This was followed by the discovery of thread-like structures in cells called chromosomes, and to the fact that the hereditary traits were located in the chromosomes. Later the chromosomes of all living things were found to be composed of deoxyribonucleic acid (DNA). Finally the molecular structure of DNA was discovered and the genetic code broken. Molecular biologists, working primarily with microorganisms, learned how to artificially manipulate DNA in cell-free systems to produce recombinant DNA molecules.

In discussions with people who are not geneticists or molecular biologists, I have found it useful to use analogies. A DNA molecule might be thought of as a twisted ladder where the two sides were each composed of phosphate and sugar groups, the connecting "rungs" being pairs of bases connected by hydrogen bonds. There are four bases and only two pairings - adenine with thymine (A-T) and guanine with cytosine (G-C).

Another analogy is useful in explaining the genetic code. The English alphabet has 26 letters. Words are formed by arranging the letters in different linear combinations. Sentences are formed by arranging words in linear sequences. As sentence follows sentence these 26 letters are capable of writing the Bible, the Constitution of the United States, Shakespeare's works, legislation, the daily paper, or anything else the mind is capable

of expressing. So it is, in a way, with the genetic code of life. There are only four letters (A, T, G, C) and all the words are three letter words. The arrangement of "words", or genetic codes, in linear sequence imparts to all living things their genetic potential. The infinite ways the code may be constructed gives to the four bases the capability of producing all forms of life from viruses to humans.

One way to place recombinant DNA technology into natural history and agricultural perspective is to utilize an outline; bear in mind this outline is concerned with the recombination of DNA in general, not just that narrowly defined as recombinant DNA.

Recombination of Deoxyribonucleic Acid (DNA)

I. Natural recombination.

In the history of the earth DNA is as old as life; DNA has been recombining since the beginning; modification through descent by variation and natural selection formed the array of genetic diversity among and within species.

II. Human directed recombination.

This activity has been practices for scientific investigations and to achieve useful objectives through plant and animal breeding.

A. Cellular

1. Sexual

a. Selection (genetic shift at population level)

The first agriculturists began to tend those plants and animals useful to them. They doubtless selected for their new breeding stocks those plants and animals which gave them the best production and quality of

product. Selection is still practiced, and it remains a powerful way to shift the genetic composition of a population. The organism selected is not changed genetically; it is allowed to reproduce, and this privilege is denied to all others in the population from which it is drawn.

b. Hybridization and selection

Today plant and animal scientists utilize hybridization to develop populations with a wide array of segregating characteristics representing almost infinite recombinations of traits from different parental stocks. By selection and evaluation and repeating the process over and over, individuals can be bred with the genetic composition (arrangement of DNA) to achieve desirable objectives. This sexual, cellular approach has been used to make great improvements in the productivity and quality of agricultural plants and animals. This approach will continue to be an important one in agriculture.

(1) Independent assortment (recombination at whole chromosome level)

At meiosis (the cell division preceding formation of sex cells, i. e., egg or sperm in higher animals or egg and pollen in higher plants.) chromosomes assort at random resulting in genetic recombination at whole chromosome level.

(2) Crossing-over (recombination within chromosome level)
Also at meiosis, chromosomes may exchange segments of DNA resulting in recombination within chromosomes.

(3) Mutation (genetic change within chromosomes)
Mutations occur naturally and also may be induced by ionizing radiation or by treatment within chemical mutagens. They represent sudden genetic changes not brought about by Mendelian recombination.

(4) Ploidy (replication at whole genome level)
Whole sets of chromosomes whether from different species (allopolyploids) or from the same species (autopolyploids) are replicated in the same organism.

(5) Interspecific and intergeneric gene transfer
Genetic material from one species can be introgressed into the genome of another if they are closely enough related for hybridization to occur.

(6) Cytological abnormalties
Unusual cytological arrangements such as inverted, duplicated, deleted, and translocated chromosome segments; irregular chromosome numbers such as one extra (trisomic), one missing (monosomic) etc. have been used to advance the understanding of heredity and to achieve desired objectives.

2. Asexual

a. Somatic cell fusion (ploidy)

Asexual methods for agricultural uses are as old as the ancient arts of making cuttings and grafts. Recently the fusion of somatic cells perhaps adds some range to the forms of life than can be hybridized. This technique has nothing to do with recombinant DNA as now defined, and it necessarily operates at the ploidy or whole genome level.

b. Cell culture and selection

Techniques for culturing plants from single cells and callus tissue opens up new opportunities for selection at the cellular level. Again this is not recombinant DNA technology.

c. Transduction

Transduction is the carrying of hereditary material from one microorganism to another or from one strain of microorganism to another by a filterable agent (as a bacteriophage).

d. Transformation

Transformation is the transfer of hereditary material from a donor bacterium to a recipient bacterium by plasmids.

B. Cell-free

1. Asexual

a. Recombinant DNA technology

With the possible exception of the cell-free, asexual technique, which has been defined as recombinant DNA, nature employs all the techniques listed under human directed recombination. The differences are that humans can speed up the process, and direct the efforts toward goals of advantage to people.

In this total perspective of recombining DNA, recombinant DNA appears as a cell-free, asexual approach. Agricultural scientists recognize that recombinant DNA technology expands the range of life over which DNA can be manipulated. This allows DNAs to be recombined among organisms which do not ordinarily exchange DNA. As the science advances it should increase the precision with which DNA can be manipulated.

Objectives for agricultural research are set primarily by the needs of people and by the problems faced in the production, harvesting, storing, transporting, processing, and marketing of agricultural products. Objectives are often set as new scientific information reveals new opportunities which did not occur to anyone before the discoveries were made.

Recombinant DNA technology will not make any major changes in the objectives of agricultural research. It offers another approach to achieving these objectives. Perhaps it will allow objectives to be reached which could not be achieved otherwise and it may make others easier to achieve.

Some possible uses of recombinant DNA technology in agriculture are under preliminary investigations, but most are in discussion or speculative stages.

Nitrogen fixation is mainly achieved by an interrelationship of certain bacteria and legumes. In view of the energy crisis and the use of fossil fuels to produce nitrogen fertilizer, it would be highly desirable if

bacteria could be found to fix nitrogen with plants other than legumes. Nitrogen fixation by bacteria in grasses has been reported. It is not too far fetched to imagine that recombinant DNA technology might be used to enhance this ability.

Biological control of pests is needed in order to reduce the dependence on chemical pesticides. For example, Bacillus popilliae attacks Japanese beetles and certain other white grubs. The difficulty is it can not be readily grown in artificial culture. Another bacteria, Bacillus thuringiensis can be readily mass produced in culture but will not attack the grubs. Recombinant DNA technology might be used to develop bacteria that are easy to culture and able to attack THE GRUBS AND other insect pests.

Ruminant animals utilize bacteria in the digestion of feed and some feed are not efficiently digested. Such bacteria might be modified to more efficiently utilize forage, and to digest feeds not now commonly fed to animals.

Photosynthesis is the process whereby green plants use the energy of the sun to convert carbon dioxide and water into carbohydrates and oxygen. Life on earth depends on this process. Some plants are more efficient than others, and possibly plant DNA could be modified to improve photosynthetic efficiency.

Scientists are learning of the internal biochemistry of cells to the point where specific enzymes for formation of proteins are known. It might eventually be possible to synthesize genes to produce a desired biochemical function and insert them into host cells through DNA technology.

Agricultural scientists intend to investigate the possibility of inserting DNA into the genomes of higher plants and animals with plasmids as is done with bacteria, and also to put plant DNA into bacteria to better

understand its functions. Recombinant DNA technology would be viewed as a supplement to, not a replacement of, many traditional approaches. Agricultural scientists would observe safe practices during all these investigations.

Agricultural scientists have made good use of the increasing understanding of the nature and function of hereditary materials. Recombinant DNA technology represents a major new development and has great potential for agriculture.

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Chairman THORNTON. Thank you very much, Dr. Lewis. I want to express my appreciation for your good testimony.

Professor George Wald has been widely and properly recognized in the DNA recombinant molecule issue as one of the most eloquent and vocal opponents of the conduct of this research, or at least eloquently stating the circumstances under which certain limited amounts of such research should be permitted. I'm not sure it's reasonable or proper to draw lines between proponents or opponents of research, but you are welcome here today, Dr. Wald.

We're looking forward to your testimony. You may proceed.

[A biographical sketch of Dr. Wald follows:]

DR. GEORGE WALD

George Wald, Higgins Professor of Biology, Harvard University, Cambridge, Mass. Author of numerous papers on vision, biochemical evolution. Honorary degrees from Yale, New York University, McGill, Berne (Honorary M.D.) and others. Eli Lilly Prize of American Chemical Society, 1939; Lasker Award American Public Health Assn., 1953; Proctor Medal Assoc. for Research in Ophthalmology, 1955; Paul Karrer Medal in Chemistry, Univ. Zurich, 1967. Nobel Prize in Physiology or Medicine, 1967. Fellow, Nat. Acad. Sciences, American Acad. Arts and Sciences, American Philosophical Society. b. N.Y.C., Nov. 18, 1906; s. Isaac and Ernestine (Rosenmann) W.; B.S., N.Y.U., 1927; M.A., Columbia, 1928, Ph.D., 1932; M.D. (hon.), U. Berne, 1957; D.Sc., Yale, 1958, Wesleyan U., 1962, N.Y.U., 1965, McGill, 1966, Amherst Coll., 1968, U. Utah, 1971; m. Frances Kingsley, May 15, 1931 (div.); children—Michael, David; m. 2d, Ruth Hubbard, 1958; children—Elijah, Deborah. NRC Fellow at Kaiser Wilhelm Inst., Berlin and Heidelberg, U. Zurich, U. Chgo., 1932–34; tutor biochem. scis. Harvard, 1934–35, instr. biology, 1935–39, faculty instr., 1939–44, asso. prof. biology, 1944–48, prof., 1948—, Higgins prof. biology, 1968—. Vis. prof. biochemistry U. Cal., Berkeley, summer 1956; Nat. Sigma Xi lectr., 1952; chmn. divisional com. biology and med. scis. NSF, 1954–56; Guggenheim fellow, 1963–64; Overseas fellow Churchill Coll., Cambridge U., 1963–64; participant U.S.-Japan Eminent Scholar Exchange, 1973; guest China Assn. Friendship with Fgn. Peoples, 1972. Recipient Eli Lilly prize from Am. Chem. Soc., 1939; Lasker award Am. Pub. Health Assn., 1953; Proctor medal Assn. Research in Ophthalmology, 1955; Rumford medal Am. Acad. Arts and Scis., 1959; Ives medal Optical Soc. Am., 1966; Paul Karrer medal in Chemistry U. Zurich, 1967; co-recipient Nobel prize for physiology, 1967; T. Duckett Jones award Helen Hay Whitney Found., 1967, Bradford Washburn medal Boston Mus. Sci., 1968; Max Berg award, 1969, Priestley medal Dickinson Coll., 1970. Fellow Nat. Acad. Sci., Am. Acad. Arts and Scis., Am. Philos. Soc. Co-author. General Education in a Free Society: Twenty Six Afternoons of Biology, 1962; also science papers on vision and biochem. evolution. Home: 21 Lakeview Av Cambridge MA 02138. *"A scientist lives with all reality. There is nothing better. To know reality is to accept it, and eventually to love it. A scientist is in a sense a learned small boy. There is something of the scientist in every small boy. Others must outgrow it. Scientists can stay that way all their lives."* (*Remarks on receiving the Nobel Prize, Stockholm, 1967*)

STATEMENT OF DR. GEORGE WALD, PROFESSOR OF BIOLOGY AND NOBEL LAUREATE, HARVARD UNIVERSITY, CAMBRIDGE

Dr. WALD. Thank you, Mr. Chairman. I'm very happy to be here. I hope there will be an opportunity, not in order to produce a confrontation, or even an argument, but to clarify some of the issues.

I hope there will be an opportunity for me to comment on some of the remarks which——

Chairman THORNTON. Well, first of all, may I say that without objection your prepared statement which I have reviewed, and which is a very excellent statement, will be made a part of the record at this point.

[The prepared statement of Dr. Wald is as follows:]

Statement Before the House Committee on Science and Technology

George Wald
(Higgins Professor of Biology, Harvard University)

It is sometimes said that those opposed to the gene-splicing technology are threatening to stifle free scientific inquiry. Not at all. The inquiry is fine. All biologists are asking the same questions, and would like to find answers to them. The problem involves only this specific technology for answering those questions.

And not even with all of that. One way of practising this technology arouses little concern. That is to restrict it to exchanging genes within single species or among species that regularly exchange genes in nature -- such as all the bacteria that inhabit the human large bowel. This is what the NIH Guidelines call the P1 level. The argument is that anything an experimenter might do at this level would have already happened innumerable times naturally. Hence there should be no novelties, no surprises.

Yet this P1 level offers one way to get at some of our most basic biological questions: how genes are turned on and off, gene control mechanisms, position effects (how the position of a given gene on a chromosome affects its expression), and the like.

There already exists a second available technique for getting at such questions, with complete control and no apparent hazard: the total synthesis of genes and their control mechanisms, such as recently performed by Har Gobind Khorana and his co-workers at MIT. This technique offers a degree of precision and control far beyond the gene-splicing technology; but it is laborious and slow.

Undoubtedly other relatively riskless ways of approaching these issues will be developed. The main arguments for plunging ahead with the gene-splicing technology at once are ease, convenience and speed.

I think that everyone concerned -- including NIH -- now agrees on three things: (1) the context of ignorance in which the present NIH Guidelines were designed; the Introduction to the Guidelines says: "unfortunately, the needed data were, more often than not, unavailable". (2) The potential biohazards; and (3) that if trouble should arise in the form of new pathogens, it will be spread abroad principally by the laboratory workers.

It is frequently said that opponents of this technology exaggerate its dangers: that they are having bad dreams. All one can say to that is

that NIH is having the same dreams. In its remarkable Recombinant DNA Draft Environmental Impact Statement (issued September 9, 1976) it is clearly stated that this technology could produce new diseases including new causes of cancer, noting also that such effects might be difficult or impossible to identify or to trace to their sources (p. 38436). Also that such effects, should they arise, would be principally spread by the laboratory workers (pp. 38432, 38436). What then is the physical containment? Also it foresees eventual application of this technology to modifying the genetics of higher animals, including man (human genetic engineering), and the very serious social and ethical problems that will raise (p. 38432).

The fact is that in our present state of ignorance, any potential benefits to be derived from this technology are at least as vague and dreamy as the potential risks. Indeed more so; for while we have not yet heard of a potential practical benefit that bears close examination, we have already encountered several examples of high risk, not realized only because the workers involved had the wisdom and restraint to stop the research (Science, 195, p. 378). Nicholas Wade ends this article with the query: "But in wielding their ever increasing powers for manipulating the stuff of life, will all biologist in the future always act with as much intelligence and restraint?

What should be done?

My own position, shared by others, comes down stepwise from maximum restraints that I would most favor to minimum restraints that seem to me bedrock in exercising public responsibility:

(1) A moratorium on the entire technology, particularly above the P1 level, to provide a breathing spell for further evaluation of benefits and risks, and to further educate both the professional and lay public.

(2) Such a moratorium could be complete, or could provide the opportunity for intensive research in one or a few well-contained, government-supervised laboratories to answer some of the most crucial questions that now plague this field, telling us better what to expect from it of good and ill. Also to develop an alternative host organism to replace E. coli, a regular inhabitant of the human bowel, and hence a particular invitation to potential trouble.

(3) Segregate this technology permanently, beyond the P1 level, to one or a few national or regional laboratories, outside cities, and not in universities where the laboratory workers regularly leave to teach classes.

The NIH Environmental Impact Statement (p. 38435) makes a very strong case for such segregation, followed by an astonishingly feeble case for diffusing this research widely, as is now happening. Note also that the pattern that is developing in Great Britain and the European countries is tending strongly toward segregation rather than diffusion of facilities.

(4) Whatever else is done, if this technology does become widespread, what is now called the P2 level (transferring genes from cold-blooded organisms into host bacteria) should be merged with and should be made to assume all the restrictions of the P3 level (now involving only the transfer of genes from warm-blooded animals excepting primates, which are P4). NIH concedes that this distinction is "controversial" (p. 38435). It has in fact little if any biological basis. It should be voided, making P3 the lowest level of containment.

(5) It is essential also to bring the work done in industry under control. Fortune magazine in its February 1974 issue already saw fit to run a long article pointing out that a multi-billion dollar industry might well lie in this direction; and that a number of the scientists involved had already established corporate connections. The pharmaceutical industry in an early meeting with Dr. Frederickson of NIH announced three sources of difficulty with the Guidelines: (a) that it hoped they would not become enforceable regulations; (b) that for competitive reasons, they could not reveal what they were doing; and (c) that whereas the Guidelines kept recombinant DNA experiments down to volumes of 10 liters, they would have for production purposes work at levels of 1000 gallons or over. Last November the industry, in a meeting with Ms. Anker-Johnson of the Commerce Department, rejected the NIH Guidelines. In a recent apparent reversal of position, they have announced acceptance of the Guidelines, and of the inevitability of legislation to enforce them.

There may however be a gimmick in this new position: a hidden distinction between industrial "research" and "production". The industry may indeed be ready to accept the Guidelines for what it designates to be "research"; but may try to evade those restrictions for what it chooses to call "production".

(6) Particular attention needs to be directed toward what the armed forces may do with the gene-splicing technology. The Federation of American Scientists (formerly the Atomic Scientists) says in its Public Interest Report of April, 1976:"Not only common sense, but the biological treaty of 1972 to which the U. S. and 110 nations have become signatory, demands

that scientists eschew development of such agents (i.e., of biological warfare). Nevertheless, since treaties are neither universal nor self-enforcing, the world must begin to face a biological proliferation threat that might before long rival that of nuclear weapons."

A last point: I doubt that scientists or others have yet taken in what the legislation that is contemplated in this area portends. It seems headed toward founding a new bureaucracy for licensing, inspecting, supervising and setting rules for the conduct of scientific research. If that happens, we may shortly have thousands of government employes who earn their livings and make their careers out of such activities. It will cost a lot of money; and once it starts, it will be hard to stop, or even to keep from growing. And it will certainly not remain confined to gene-splicing. Indeed the proponents of gene-splicing have laid the ground for its expansion to all other fields of experimental science. They have announced repeatedly that all scientific research, that all exploration of the unknown, is risky, carries potential dangers. And when I have said in reply that I had never done a dangerous experiment, they have answered, "Oh, no? Don't you use alcohol? Isn't that inflammable?"

That kind of argument has make all experimental science highly vulnerable. A new, self-promoting bureaucracy could go far into complicating, impeding, tying up much of what has always gone on, and safely, in research laboratories of every kind. That really would end by stifling free scientific inquiry. It would be the end of American science as we have known it.

I believe that widely diffused gene-splicing beyond the P1 level absolutely demands adequate government control, effective and enforceable, in research laboratories and industry. There is a simple solution to this dilemma, already stated above. It is to segregate such work, above the P1 level, to one or a few regional laboratories, out of cities and universities, and so readily contained and controlled internally. All the supervision could be maintained in those few places, and scientific work of every other kind could go on unhampered throughout the nation.

George Wald

Higgins Professor of Biology, Harvard University,
Cambridge, Mass. 02138

March 29, 1977

Chairman THORNTON. We would be pleased to hear from you right now, to summarize that statement, or to make such comments as you feel are appropriate.

Dr. WALD. Well, perhaps I should begin by summarizing the statement, and then see where we come out.

Chairman THORNTON. Fine. Please proceed.

Dr. WALD. Yes.

First of all, I should like to say something that involves what to me, as a lifelong biologist, is the major problem that is hardly ever addressed at all. That is that this recombinant DNA technology puts into human hands the possibility of redesigning technologically the products of 3 billion years of evolution on this planet, crossing the widest barriers that now separate living organisms—in fact beginning by crossing such a barrier: that between bacteria and higher organisms.

And it's a genuine and very serious question, whether we wish to put into the hands of any group of persons an unlimited capacity to tamper with, modify, redesign, in fact technologize, living things on this planet. That I do regard as the major issue.

But, as I say, it hardly comes up, and very possibly will not arise within the work of your committee.

Chairman THORNTON. Well, I think that we are making an effort here to address the broad public issues which are involved in this.

Dr. WALD. Yes.

Chairman THORNTON. And we're not limiting our inquiry to specific legislative proposals, but we are seeking an input of thoughtful analysis and reflection, and we appreciate your contribution.

Dr. WALD. Well, I'm happy to hear that.

It's often said that persons like myself, who are opposed in various degrees to the widespread use of this new technology, are inhibiting free scientific inquiry. I think that's a misunderstanding.

The inquiries are fine. All biologists are asking the same questions. The only conflict involves the use of this specific technology to try to answer those questions.

I was very grateful for Maxine Singer's careful presentation of already-existing alternatives. I think she is a superb teacher. I say that as a teacher. I hope she goes on teaching. I think that the statement of the present position of the alternative procedures is absolutely fair.

One should not by any means shut off the probability that shortly we will have further procedures and further, relatively riskless procedures. That is an important consideration. Meanwhile, the term recombinant DNA is bandied about as though it were just one thing and you either took it or left it. No.

As I hope everyone gathered from her presentation, there is a level at which there is little concern with recombinant DNA work, and that is the level designated by NIH as P1. As long as one keeps these experiments restricted to exchanges of genes within one species or among those species that regularly exchange genetic material in nature, such as all the bacteria that inhabit the human bowel—as long as one confines this research within those boundaries, there is little concern with it.

And second, as she quite fairly said, we can approach some of the most important biological questions at this level; and I would hope shortly perhaps approach at this level work with higher organisms.

Everyone concerned with this work has by now come to certain common agreements. Everybody knows, realizes—and that's come up repeatedly in the course of this session—that the NIH guidelines were formulated in a context of fantastic ignorance of what to expect, what these directions of research might have as consequences. And I was happy on the plane down here this morning to see that at NIH and at Fort Detrick plans have now been laid to address some of the most crucial questions; so that really the call for at least a temporary moratorium at present on this kind of research is just simple prudence.

Shortly we can hope to have some of the answers to these questions that now we don't have at all. So that the context of ignorance is something that everyone agrees on.

The presence of potential biohazards is the second matter of agreement.

A third matter of agreement makes a rather striking commentary on so-called physical containment. It is agreed throughout—we have had this laid out by the proponents of this research at Harvard endlessly; and the NIH environmental impact statement comes back to it again—it is agreed throughout that if trouble arises—and all of us hope that it won't—that if serious trouble arises it will be carried out of the laboratories principally on the workers.

To me, that's a very serious blow, that universally-conceded fact, to all our concepts of physical containment.

I think also that when this committee addresses the matter of those persons principally in risk through this research, it should be careful not to confine its considerations to the laboratory workers alone. The janitors in the building, the stockroom people, are perhaps even more exposed and more ignorant of the necessary precautions than the laboratory workers.

Frequently, it's alleged, and there were implications throughout the discussion this morning to that effect, that the people who are in opposition, particularly those like myself who work in other fields of biology, are having bad dreams, having nightmares. Well, I want to say something about that: NIH is having the same bad dreams. I've said that in my paper that has been given you.

One of the most remarkable and interesting documents I have encountered is the draft NIH environmental impact statement. And everything, everything, that has been brought up and usually brushed aside in the way of potential hazards is considered seriously and said plainly in that statement, including the possibility that this technology will produce new cancers. My own betting in the cancer situation—and it's no more than a bet—is that it's more likely to do that than lead to cures in existing cancers.

Also one must not leave out a consideration—and the NIH draft impact statement says this perfectly plainly—that what lies ahead through this technology is the manipulation, the redesign, of the genetics of higher organisms, including man, so-called human—what's the term? Genetic——

Dr. LEWIS. Engineering.

Dr. WALD [continuing]. Engineering. Thank you.

Human genetic engineering. And as for how far off this is, it's anyone's guess. But one of the principal, and most eloquent, and expert proponents of this technology, David Baltimore, in a hearing before

the Cambridge Review Board, startled me as this human genetic engineering possibility was brought up, by saying with a little irritation: "Why talk about that now? That may be 10 years off!" Ten years seems a long time to him.

I've tried to say in my prepared statement, what it is I think needs doing. I want particularly to stress a few points.

One of them is that—and I must say I've heard this argued back and forth and become more and more convinced—the necessity, whatever else is done, to apply all the restrictions now on the P3 level, to apply them all at the P2 level.

You understand, I think P1 is sort of home free; that is what I defined before, exchanging genes within one species or between organisms that regularly exchange them in nature. The argument there, incidentally, is perfectly simple. It's that no surprises are to be expected, that anything an experimenter does within this limitation will have happened innumerable times in nature.

I don't agree with Dr. Lewis on some other things that he has said, but on that degree I think this is true. So, to jack up the P2 level to P3 I think is a very serious need.

The NIH environmental impact statement singles out this distinction between P2 and P3. Perhaps I should say what these terms mean. The P2 level means shifting genes from coldblooded organisms into some bacterial host, say *E. coli*. P3 is shifting them there from warmblooded organisms.

The NIH environmental impact statement concedes that this is a controversial matter, and I think myself, as a lifelong biologist, that it has no substantial biological basis.

Second: I want to say also that one should not concentrate one's thinking upon what goes on in medical and university laboratories. There are 86 such laboratories, incidentally, now contemplating doing recombinant DNA research, and at least nine pharmaceutical companies.

I want to say a few words about this industrial tieup, because it involves a consideration that I think needs very much to be clarified factually.

It is this: Early on, leaders in the pharmaceutical and chemical industry met with Dr. Frederickson, then Director of NIH, and pointed out that though they were for the guidelines in principle, that they had three things that they objected to. One of them was that they hoped that the voluntary guidelines would not become enforceable regulations. The second point was that they could not live with the restriction of recombinant DNA experiments within the guidelines to 10 liters, approximately 10 quarts; that for production purposes they had to go at the level of at least 1,000 gallons.

Third: That for competitive reasons they could not say what they were doing.

Very recently, they seem to have reversed this position, and it's that that gives me particular pause. They seem to regard legislation as inevitable now, and if I understand correctly what they've been saying, they are ready to accept the NIH guidelines. So that puzzled me very much.

At the National Academy of Sciences meeting about a week and a half ago, I tried to get this clear. I did it in personal conversation,

so that it never came out in the meeting; so let me say it here. I fear that there is a hidden—I say hidden because it was not expressed, publicly, though I asked please to express it at that meeting—a hidden distinction between recombinant DNA research and production.

The industry seems to have its own ideas about this. Now they say—a reversal of position, since last November 19 the leaders in the pharmaceutical and chemical industry met with Anker-Johnson, an official of the Commerce Department, and flatly rejected the NIH guidelines—when they say now, as I understand they're doing, that they accept them, I would gather from this conversation that they have a little gimmick in mind, and that is that they are accepting them for so-called recombinant DNA research, but they have something else on their minds when it comes to production. There I am afraid that they are still having and pushing the same concerns as previously.

I put enormous importance, but I don't care to add to the statement you have in your hands, on the interest that is very likely going to be taken by the Armed Forces in the potentialities in this research. And in that connection, I would like to leave some copies of the document that I cite, which is something you may find valuable also as a general discussion of both sides of the subject of DNA.

Chairman THORNTON. We appreciate your furnishing this material to the committee. We will review it.

Dr. WALD. It's from the Federation of American Scientists, a by no means radical organization, and this military possibility is discussed very plainly and hardheadedly by members of that organization, some of whom have had close previous connection with the Department of Defense.

[The document was distributed.]

Dr. WALD. Could I take a couple of minutes to raise some points that came up from my colleagues.

Chairman THORNTON. Please. As a matter of fact, with the consent of my colleagues up here, I will use my first 5 minutes of inquiry to make available to the panel an opportunity to comment with regard to the testimony presented by each of the other members of the panel.

If you have comments, I think it might be appropriate to get that kind of exchange at the outset before we begin to ask our specific questions.

You may begin, Dr. Wald, with your comments.

Dr. WALD. Thank you very much.

I was very much relieved, I may say, and full of admiration with Dr. Singer's teaching of all of us; very much relieved also that she spoke, among the benefits of this research, only of the scientific benefits, not of the practical benefits of which we have heard so much.

I must say, having tried to search out those practical benefits as well as I can, I have yet to hear a scenario, including, I'm afraid, Dr. Lewis' hopes for nitrogen fixation by grain plants, yet to hear a scenario that will bear close examination.

I think everyone is now agreed that the only sure benefits are going to be the clarification of some basic biological problems.

I want to go at once then to Mr. Barkley's testimony, because it raises some very serious issues that are frequently glossed over. He commented—he quoted directly from, I understand, his former master,

Dr. Wedum—I hadn't heard, and I'm sorry to hear that Dr. Wedum is no longer with us—but Wedum wrote a report on the operations at Fort Detrick for the DNA Advisory Committee that designed the guidelines.

In that report, he said that there were 423 infections and three deaths in 25 years of operation. Everyone, all the proponents at this point, point out that there exists no clear instance of a transmission of disease beyond the laboratory workers at Fort Detrick. Well, that's a good argument for keeping this kind of research in Fort Detrick.

But let me say, in addition, that there has been a startling lack of information in this regard. There is no system whatsoever—it's never been asked for—of reporting diseases that might have had this kind of origin, nor any checkups. We simply don't have the information. And you have to estimate as best you can a situation in which we have no solid information, and none has ever been sought. There was never a system, as I understand it, of checking up on the health of either workers or their families systematically, or keeping reports, as I understand it. That kind of information has not been sought out. Perhaps Mr. Barkley would care to refute that view, but that's the situation as I understand it.

Now, I want to say one thing more, terribly important it seems to me, and that is along the general theme which I've heard endlessly: "Everything's under control, we know how to handle diseases;" and so on. I want to say three simple things:

Statement 1: This technology is going to put into the hands of biologists all over the country the possibility of dealing with pathogenic organisms which they have no experience with and no previous training. We are turning over this possibility of having to deal with pathogens—I'm talking of my colleagues in my own Department at Harvard—to people who have no experience and no training in this direction.

Second point: We're not talking of old pathogens. We're talking of brandnew pathogens.

Third point: When a new pathogen arises, the most experienced workers with pathogens die like flies, and——

Chairman THORNTON. Dr. Wald——

Dr. WALD. Yes?

Chairman THORNTON. Is experimentation in recombinant DNA allowed to proceed with regard to pathogenic organisms?

Dr. WALD. Well, first of all, no one knows what to expect. I'm about to say that.

But, second, as NIH and everyone has recognized from the start, among the potential dangers is production of new pathogenic——

Chairman THORNTON. Isn't experimentation with pathogenic organisms strictly prohibited?

Dr. WALD. But the possibility is offered by this technique. We don't really know——

Chairman THORNTON. Right.

Dr. WALD [continuing]. What makes an organism pathogenic.

Chairman THORNTON. And——

Dr. WALD. Nor do we know at this point—nobody knows—how epidemics start or, even more interesting, stop. So we are talking of

the possibility—I'm not talking of the use of known pathogenic organisms, but the production of new pathogens. And what I'm saying is with new pathogens, when they come up in the most experienced hands, these people die like flies.

The green monkey disease, the Marburg disease mentioned before—of 30 technicians handling it—Marburg, Germany, you know, those experienced German technicians—of 30, 7 died. It's now sweeping across Africa.

Lassa fever, discovered in 1969, 2 nurses died; 10 out of 21 medical workers have recently died, including the woman doctor, Jeannette Troop [phonetic], who first put the finger on this.

Another point: This entire guarding against doing wrong things with pathogenic organisms relies on a table of what organisms are pathogenic and how pathogenic they are. Let me say that this is full of loopholes. There is a red bacterium call Serratia marcescens. My wife worked with gallons of this stuff. It is not a pathogenic organism. The Army sprayed that stuff into the air and the sea north of San Francisco in 1950—and incidentally with every assurance that it couldn't survive. In 1951, a brandnew disease appeared in San Francisco. It's called Serratia endocarditis and between 1969 and 1974 when my own information ends, there were 19 cases in San Francisco, 13 fatal. The mortality is high.

We were sure that organism was not only not pathogenic but that it wouldn't survive. It found itself a place to survive. Out of those 19 cases, practically all of them were shooting up drugs; and whether it's the shooting-up process or whether it's the debilitation that goes with it, no one yet knows.

Roy Curtiss and biological containment. The main problem here is not how long those so-called crippled bacteria will survive, but whether or not—and no one yet really is ready to answer that one—while they survive they will exchange genetic material with noncrippled bacteria, including noncrippled E. coli. That's really probably the most serious issue.

As to their survival, it's pretty thoroughly up in the air. The testing in this regard of K–12, this EK1 organism, is pitifully meager. I was amazed to hear, with all this weight being put on it, how little of that has been done.

You must bear in mind that there are particular instances in which perhaps crippled organisms that wouldn't survive in our large bowel will survive where there is no competition—in the bowels of persons that offer such organisms little competition. What are they? Young infants, who are born with sterile guts. We have a whole history of special pathologies in the newborn—the nurses, the adults, the parents are perfectly safe; it's the newborn who are susceptible.

People who have just passed through a course of antibiotics or sulfa drugs, that have cleaned out their normal bowel populations of bacteria.

So there still are big problems in this situation. Incidentally, one of the great messages that has come through for bacteria and viruses is they keep changing their properties. And I think Dr. Curtiss should shortly tell you how often and how thoroughly one needs to check the maintenance of properties in crippled—so-called crippled—bacteria.

That brings me to Dr. Lewis, and there I think—forgive me, Dr. Lewis—but I think you've perhaps confused a little the natural situation and the artificial ones that have previously involved crossing organisms—so-called artificial selection, in which one breeds animals and plants to satisfy human desires and needs—that is, animal and plant breeding in domestication.

I think all that stuff I've ever heard of is P1. That is, these operations are conducted within one species, or within very closely-related species, in order for them to work at all. Perhaps you can straighten this out.

Dr. Lewis also mentioned among the possible benefits one that has turned out to be not probably feasible. You understand that both benefits and risks are said to be in the category of dreams. But we recently had an article in Science magazine that pointed out that three really dangerous things have already come up in recombinant DNA work. I say that in my presentation. But I didn't tell you what they were. And since Dr. Lewis, if I understood him, brought this up as one of the hopes, I'd like to spend the last 2 minutes to tell you what it is.

It was the work of Chakrabarty, the man who works in the research labs of General Electric, and his first triumph was to produce—not E. coli this time—but another bacterium, Pseudomonas, that could completely digest petroleum.

It was pointed out at once how useful this might be to clean up oil spills. As I pointed out elsewhere, how about oil that hasn't spilled? We have to worry a little about letting loose a bacterium that feeds on petroleum. But Chakrabarty had another success.

He suceeded in putting into E. coli the gene for the enzyme cellulase, that can digest cellulose—cellulose, the stuff of wood, the stuff of paper. Your first thought is, "Oh, great!" The unit for making wood and paper, as it is for making starch, is the sugar glucose. Your feeling is, "My heavens! We could all have our lunch just eating Kleenex." Then the second thoughts come up. Chakrabarty had those second thoughts. After all, that E. coli lives not in the small intestine where glucose is absorbed, but in the large intestine where the absorption has stopped so it would not be absorbed. Meanwhile, it would clean out all the roughage, and we can't live without the roughage in the intestine. There would be hopeless diarrhea as a result if we didn't have that roughage.

So it would digest the roughage, producing glucose which we can't absorb; and then other bacteria in that gut could turn that glucose into methane, an illuminating gas. With that, Chakrabarty realized that was a pretty dangerous organism, and he destroyed his cultures. It's an interesting example of another supposed benefit gone wrong.

Thank you, Mr. Chairman.

Chairman THORNTON. Thank you very much, Dr. Wald.

I am pleased to note that what I had thought to be an original thought of mine at some hearings some weeks, or perhaps months, ago about the possible concern of getting up and going out to the automobile and finding a tankfull of harmless bacteria was one that you had also been speaking of.

I think it is also important to recognize that cattle, for example, are enormous manufacturers of methane. The four-stomach system of a cow and the bacteria which live there produce something like 50

cubic feet of methane per day per cow, and isn't a particularly destructive organism as far as that particular animal is concerned. It is equipped to handle that. A human being would not be.

I also think it would be appropriate, before opening to other panelists, to observe that the Lassa fever, which is experimented with in P4 containment facilities, is not a result of biological DNA recombination, but is a naturally occurring organism which is extremely dangerous, and which does require the highest levels of containment in order to do the research on it.

And one final observation is that the transformation which you described in the San Francisco Bay area in 1950 and 1951 was also prior to human efforts at least at recombination of DNA, and is not an event which is related directly to DNA recombination.

With those observations, I'd like to ask Dr. Singer if you have any comments.

Dr. SINGER. Thank you.

First, a brief comment about the oil-eating bacteria, because this is a story which many people tell and use. I think it's important to recognize that the bacteria in question are strict aerobes and must have oxygen in order to live. They would certainly not find oxygen in the oil wells which people imagine they might go into and devastate. I think that's an important matter in considering this particular experiment.

But, more generally, I would like to say that it was very interesting to listen to Professor Wald this morning, in particular, because I realized for the first time that in many discussions there are very, very broad areas of agreement between those who are characterized on one side of the fence and those who are characterized on the other. In fact the areas of agreement are broad enough as to make those characterizations really counterproductive to all of us.

In particular, I share Professor Wald's statement that if the recombinant DNA technology leads to the opportunity to redesign living things, to do what is called genetic engineering on whole complex organisms and not simply on bacteria used either in a laboratory or in a production plant to achieve particular ends, then there are very serious societal problems that need to be addressed and need to be addressed in the widest possible forum in order to inform both public decisions and private decision. And I would say that we should develop mechanisms for that discussion. However, I would separate that discussion from what we are now calling recombinant DNA, even though these techniques may lead to that capability.

I was encouraged to realize this morning that Professor Wald spoke about experiments within the framework that was used in devising the NIH guidelines—not because I think that's the only framework for considering the problem—but because I think it's a reasonably good one and helps us focus on isolated and specific problems. Thus, Professor Wald indicated that there are certain experiments which no one believes represent any particular new kind of harm; and, on the other end of the spectrum, there is a group of experiments which most of us agree ought not to be done at the present time. And, in fact, such a group of experiments is prohibited in the NIH guidelines, including some which people have imagined might lead to the production of cancer by recombinant DNA organisms.

So we're left with the problem of discussing the classifications and our concerns about the risks of other experiments, the ones that fall in the middle.

I think it is possible for any one of those experiments to construct a scenario which leads to an effect which we would all agree is undesirable. But simply saying that that effect is a possibility is not enough. One has to look at the likelihood that it will happen. I don't think that it's enough to say that we all have bad dreams. We have to try to deal with those dreams in a realistic way.

And so, while we can all agree that certain scenarios might occur, we really need to address ourselves to the possibility that certain things may occur. This gives us some basis for action, for saying these experiments we don't want to do, these experiments we can do, certain other experiments we need to do but do very carefully, and then trying to match the level of containment with the likelihood of indeed producing a pathogenic organism in a given experiment.

I feel that this is an appropriate way to ocnsider the problem because it allows you to make decisions about different kinds of experiments based on the relative benefits and the relative risks.

Chairman THORNTON. Thank you, Dr. Singer.

Dr. Curtiss?

Dr. CURTISS. Thank you, Mr. Chairman.

I share agreement with much of what Dr. Singer has said, but I would like to address myself to a couple of specific points raised by Professor Wald.

One of these is the likelihood of converting *Escherichia coli* K–12 into a pathogen. There is a substantial amount of experimental data that are available and published, as well as much new information which is not yet published, which I think is unfortunate at times like these.

Pathogenicity can be construed to be a composite of three attributes:

One is the ability to be communicable; that is, for the organism or infectious agent to go from one individual to another. Enteric organisms like *E. coli* and enteric pathogens like *Salmonella typhi* which causes typhoid and *Vibrio comma* which causes cholera, are transmitted by ingestion of contaminated water. Most such enteric diseases are quite well controlled by sanitary engineering in this country. We have very few problems with diseases like cholera, dysentery, typhoid, et cetera, and certainly not any epidemics of major proportions.

Another attribute essential for pathogenicity is colonizability. That is, the organism that is going to cause disease must establish itself in some ecological niche so that it can do its harm. In the case of enteric pethogens, this means that they must establish and reside in the intestine, or gain other attributes so as to occupy a new ecological niche such as by penetrating the cells of the intestinal mucosa and thus get into the circulatory system.

In the case of *E. coli* K–12 it is a laboratory-adapted strain—in fact, it's even addicted to the food in the research laboratory. It lacks certain properties on its cell surface which are normally found on *E. coli* strains that inhabit the gut. And, indeed, when we add genetic information to *E. coli* K–12 that should facilitate colonization of the intestine, and which does so in *E. coli* pathogens that infect pigs, humans, and calves, *E. coli* K–12 does not colonize.

That is because the newly produced substance that promotes colonization by *E. coli* pathogens has no anchor on the *E. coli* K–12 cell surface.

Another attribute which is necessary for pathogenicity is some mechanism to overcome host defense mechanisms—by, for example, the production of some toxin or pharmacologically active substance. I think the likelihood that one could introduce in a recombinant DNA experiment all of the genetic information necessary to endow *E. coli* K–12 with communicability, colonizability, and then mechanisms to overcome host defenses which would interfere with normal host functions is extremely remote, almost to the point of it being an impossibility on statistical grounds.

In terms of the potential to transmit recombinant DNA from *E. coli* K–12 strains or from crippled *E. coli* K–12 strains, we've done a substantial number of experiments to measure this—and these are data that are not yet in the literature.

We have calculated that for EK1 host vector systems—and this is based in large part on experiments done in the laboratory—the transmission of a nonconjugative plasmid residing in one strain of *E. coli* into another one, which requires three micro-organisms to interact in a special way, might occur in somewhere between 1,000 to 10,000 humans of the total 4 billion humans present in our biosphere per day. This is taking into account the total populations of *E. coli* in the intestinal tracts of all humans in the biosphere.

So, it is a very low probability, but it is a measurable one, and I think it does cause concern to some individuals.

The other point that I would like to mention concerns Dr. Wald's comment about *E. coli* containing cancer virus genetic information causing cancer. The point is that viruses are designed to infect cells of a susceptible host. They have evolved that way.

E. coli, on the other hand, does not have the potential to infect cells in the intestinal mucosa. Furthermore, we know that the naked DNA of a humor virus has a very much reduced possibility of infecting a mammalian cell, and indeed only occurs in the laboratory under very special conditions in which the experimental procedures are manipulated to get the desired effect.

So, I have come around to the opinion that the safest place to work with the DNA of a virus genome may be in *E. coli* and not in the virus. And although one has no data to substantiate that one belief, I think it is well founded on many years of working with viruses and bacteria and the information that's been learned from experiments conducted long before recombinant DNA technology was developed.

Thank you.

Chairman THORNTON. Dr. Barkley?

Dr. BARKLEY. Thank you, Mr. Chairman.

I would like to make just a few comments.

I think it is quite true that there is a lack of effective reporting of laboratory-acquired infections. This has certainly been so with 100 years of microbiological research.

Most reporting acquired infections have been on a voluntary basis. You may be familiar with the work of the late Dr. Sulkin and Dr. Pike in collecting laboratory-acquired infection data. Their collection

may include 50 percent of all such infections that have occurred in this country over the last 50 years.

The information we have acquired, however, from these reports has helped to indicate the manner in which infections have occurred, and they have demonstrated the need for development of effective control measures. Also, the 25 years of experience at Fort Detrick has contributed greatly to our understanding of the causes of laboratory-acquired infections. Accidents were reported, were recorded, and were investigated. It was through the occurrence of laboratory-acquired infections that methods for control were developed. This experience and knowledge can be used to select appropriate safeguards for handling recombinant DNA molecules. It is also true that we do not know if organisms containing recombinant DNA molecules have the potential to cause disease.

The selection of safeguards must, therefore, be dependent on an assessment of the potential to create a hazard. The appropriateness of physical containment measures to serve as effective safeguards is therefore not only dependent on the proficiency, knowledge and training of the laboratory worker, but is also dependent on the adequacy of the classification of potential hazards. It's this subject that so many scientists have been debating over the last couple of years. I feel that those scientists who have been debating this issue have all attempted to err on the side of safety, so that maximum appropriate safeguards would be instituted.

I also want to emphasize again that physical containment measures are not infallible. In my testimony I indicated that the most sophisticated means of control are subject to human error and so it is important that training be an integral part of this effort. I think it's also important to recognize that training is even more important for scientists involved in recombinant DNA technology because many of these scientists have not had formal training, nor have they acquired experience, in handling hazardous biological materials. They have also not had experience in using physical containment equipment. But this has been recognized, and I think efforts are at hand to pursue this important area.

I feel that the knowledge that we have acquired from the study of human disease agents provides us with a framework for selecting appropriate physical containment safeguards and a framework for assessment of potential risks of newly discovered micro-organisms.

Chairman THORNTON. Thank you, Dr. Barkley.

Dr. Lewis?

Dr. LEWIS. Thank you, Mr. Chairman.

I think the reason I tried to put an outline in my prepared remarks was to show that recombinant DNA is not the only way that we can recombine DNA. As a matter of fact, DNA's been recombining, as I said, since the beginning.

Agricultural scientists, at least, have been directing that recombination certainly throughout this century, with the knowledge of the chromosome theory of heredity.

It is true, as Dr. Wald suggested, that we have been limited in what we can combine, pretty much to what we can hybridize sexually. But within those limits we have a wide range of recombinations that we can make, and this extends as far out as what taxonomists call species and genera.

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It is not uncommon to hybridize different species of plants, and occasionally as far out as genera. And, as he pointed out, there haven't been any unpleasant surprises in that. If we've learned anything, it is that the plants and animals that are still on this Earth after all these millions of years have had to survive through competition and selection and the ability to reproduce. They represent very finely tuned genetic systems.

If you tamper with that system very much with outside, discordant combinations of DNA, you get abortions, sterility, weakness, and you do not get an instantaneously adapted organism. It's very difficult to recombine DNA's of different things and different forms and get anything that's competitive in an agricultural sense out of it.

Now, as far as the objectives at the end of my remarks, nitrogen fixation and photosynthesis and other things, we are never certain with the recombinant DNA technology or traditional technologies when we set out to achieve a complicated objective that we will ever succeed. But it's the nature of science that you have to try.

We have a success and failure rate, but on balance the agricultural effort has paid off handsomely. So we wouldn't want to leave you with the impression that we would achieve all of these objectives, and certainly we won't achieve any of them quickly.

The point I'm trying to make is that as understanding of genetics has advanced it has been possible for agricultural scientists eventually to figure out a way to utilize that for the benefit of us all.

Chairman THORNTON. Thank you very much, Dr. Lewis.

Mr. Hollenbeck.

Mr. HOLLENBECK. Thank you, Mr. Chairman.

One of the primary concerns that I've heard expressed by legislative opponents, especially of recombinant DNA research, is that we may force evolutionary changes or other changes which may be harmful.

In the last couple of days I've come across writing concerning a recent report and some recent remarks made concerning DNA research. The remarks were made by Dr. Robert Ryan at the NIH Endicrinology Conference a couple of weeks ago, and the report is by basically an English research team, including Messrs. Crick, Brenner, Klug, and a young gentleman named Pieczenik from Rutgers University. Now, these two reports and series of remarks—which I haven't seen, but which I understand are very highly technical—seem to suggest a hypothesis that recombinant DNA sequences have evolved due to natural selection process at the molecular level long before organisms had developed, and that they then would be resistant to any attempts to recode their sequence.

Now, if this hypothesis is true, and that is, basically, that nature has is own recombinant technology, would that serve possibly to alleviate some of the concern about inadvertent and dangerous evolutionary changes?

I'd like some discussion or some remarks from the panel on that; and also, you can address yourselves to the additional question on the significance of this particular work I've mentioned vis-a-vis the DNA issue in general.

Dr. CURTISS. Well, I'm not familiar with the talk because I wasn't at NIH a couple of weeks ago. I don't know whether that hypoth-

esis you mentioned will or will not be borne out, but I think there is related information that is relevant to the discussion of apprehensions about recombinant DNA research.

The point is that during the course of evolution, there is a tendency to throw away or alter that which is not needed and to maintain that which keeps the organism's lifestyle most suitable in terms of the environment at that time. Thus, one could introduce many types of genes specifying many different types of proteins into an organism. It's not likely, however, that an *E. coli* synthesizing hemoglobin, for example, is going to find much need for hemoglobin; in fact, the hemoglobin might clog the system so as to make the organism very sick, indeed.

In this regard, there are some experiments that are relevant. Dr. Ronald Davis, at Stanford, and also Dr. Stanley Cohen, at Stanford, have independently done a number of experiments in which they have put random DNA fragments from a variety of organisms, including the fruit fly, yeast, and certain other bacteria into either bacterial virus or plasmid cloning vectors, and then introduced those into bacteria to see how they compete with each other.

They probably tested over 1 million recombinant molecules in this way, and in no instance did the plasmid or bacterial virus vector containing a foreign DNA insertion out compete the original vector that did not have the recombinant DNA.

These observations, although from a very limited sort of experiment, gives me assurance that it is not likely when a gene is introduced into an organism that the organism is going to want to keep it and to become better adapted for survival in the environment.

There would be some probability in which a gene will contribute better survival potential, but it may well be less than 1 in 1 million, and that is an additional margin of safety in recombinant DNA research.

Dr. SINGER. I don't know what Dr. Ryan spoke about. I have read a preprint of the paper by Crick, Klug, Brenner, and Pieczenik, and it's my understanding that if their hypothesis turned out to be true, it would be basic to the function and structure of all DNA's and not distinguish between different organisms. Therefore, I'm not sure it would be relevant to the current problem with regard to the general discussion of the possibilities of longrange evolutionary changes resulting from the inadvertent release of organisms containing recombined DNA from distantly related species.

That's an argument which I have heard, and which I have tried to study. But I have a great deal of trouble myself in thinking that through in scientific terms. If the argument is related to the evolution of bacteria only, then it's simpler to understand and it presumably would have to do with the ability of the recombined genes to be transferred to other bacteria.

But if, as seems to be implied very often in the argument, the concern is with evolutionary changes in whole complex organisms, then I have a great deal of trouble understanding the mechanisms by which it might arise. The primary reason for this difficulty is that, even if recombined DNA were to get out of a bacterial cell in someone's gut, for example, into the cells of the living organism and do damage to

that organism, this is a different situation from a change which would be maintained in an evolutionary sense.

In order for this to occur, the change would have to be in the germ line cells. Germ line cells mature in a developing fetus, which is a highly protected organism, and the germ line cells are very protected within that organism. It's hard for me to imagine a route by which a recombinant molecule would make its way to such an organism and, therefore, I feel that an evolutionary change resulting from inadvertent release of recombinant molecules, or recombinant-containing organisms, is so unlikely as not to warrant very serious discussion.

Dr. WALD. Just a postscript to——

Chairman THORNTON. Dr. Wald?

Dr. WALD [continuing]. To Dr. Singer's last remark. We have had for many years now the technology of pushing a whole nucleus from an ordinary body cell into an egg cell, and this has been done with a variety of organisms. There are people anxious to pursue this technology to the human level. In fact, I understand that there are workers in England who are doing this.

The highest level previously has been to—well, it was done originally with frogs; but it would be perfectly possible to do with mammals, and possibly with human beings.

You understand what I'm saying: One can get into the germ line, and that is the way to do it. And all this talk about human cloning, that still, is pretty much in the realm of science fiction. Nevertheless, it's being worked on.

Mr. HOLLENBECK. Dr. Wald, I had a question for you specifically.

Dr. WALD. Yes.

Mr. HOLLENBECK. If we are to ban or put a moratorium on DNA recombinant research and slow down the pace of genetic research in this country, what would be the implications for the U.S. role in science, vis-a-vis the rest of the world?

Dr. WALD. The rest of the world is watching us now. There are nine nations at the moment that are following through this kind of argument in parallel: The United States, Britain, and I think seven European——

Dr. SINGER. And Japan and the State of Israel.

Dr. LEWIS. And the U.S.S.R.

Dr. SINGER. And Canada.

Dr. WALD [continuing]. And the U.S.S.R., of course. And so this argument is getting to be worldwide, and there are already five international organizations working on it, to design some kind of international agreement.

The simple truth of course is that if some trouble should arise—and may I say once again all of us hope it won't—it won't respect any geographical boundaries. So one can watch right now this whole business, going very rapidly from the level of towns to the State, to the Nation, to the international level.

One of the things that some people have expressed fears about is the operation of a kind of a Gresham's law in this regard. That is, that people who want to do this kind of thing, including industry, will go wherever the restrictions are least heavy.

Mr. HOLLENBECK. Thank you.

Chairman THORNTON. Mr. Krueger.

Mr. KRUEGER. Thank you, Mr. Chairman.

We certainly thank this distinguished panel for appearing with us today.

I suppose that, in part, what we are doing is this: That some of us who have had freshman chemistry and not much more are trying to sit in some sort of judgment on probabilities. And as I assess these probabilities, I notice that two of the five panelists, including one from the National Cancer Center, are both smoking. And, therefore, I assume that people are willing to engage in a variety of probabilities and possibilities with regard to health. Of course, that is generally self-directed rather than externally directed, and, therefore, it's probably not of such a large significance.

But I wonder whether I could get some people on the panel to try to give some kind of sense to those of us laymen who are trying to participate in these decisions, some sort of percentage of what kind of chance you think there is of some sort of grave genetic damage being done that would or could be passed on or be inheritable, and might then, in turn, affect human life in an adverse way.

I realize that you are going to be wild guessers, but so are we if we try to legislate. And so I would ask if you could at least hazard such a guess—a couple of the people on the panel might hazard that.

Dr. Wald?

Dr. WALD. I'm in no position to hazard such a guess at all, and I wonder what other members of the panel would say in that regard.

I don't think, realistically, that the possibility exists for answering your question. But I'm barging in only to point out a close parallelism with the situation involving nuclear power. We had a thing called the Rasmussen report from the chairman of the committee who drew it up, Rasmussen at MIT. It was to try to do exactly this, exactly this, estimating the possibility of major accident in a nuclear powerplant.

It was called Wash-400 as I recall. It ended up as a government document. Of course, it cost a lot of money, and most of us paid no attention to it whatsoever because, there again, the intangibles are so many and so strong that the possibility of making a reliable estimate doesn't exist.

Mr. KRUEGER. Dr. Singer

Dr. SINGER. Yes. I heard the question as a very circumscribed one. You asked specifically the likelihood that such experiments could lead to some change in human genetic constitution.

Mr. KRUEGER. Yes.

Dr. SINGER. Talking strictly about the kinds of recombinant DNA experiments that I described, and leaving out for the moment the sorts of experiments that Dr. Wald just recently alluded to involving the purposeful mixing of nucleii and cloning of whole humans, involving, I would say, the likelihood of making a permanent genetic change in whole human organisms is vanishingly small. However, I can't put a number on it.

I think this is very different, however, from the possibility of creating an organism that might make living things, human or otherwise, ill. This has a higher probability of occurring, but, again, I would be unable to put a very hard number on it.

One can go through an exercise of identifying the events that need to occur between the laboratory experiment and an illness in some species in an effect to arrive at such a number.

One could try to analyze the events and come to some estimate of the probability of occurring, but such estimates would be very soft.

Mr. KRUEGER. I see.

If it is just too difficult to put numbers on this, let me then inquire whether as we go at least through procedures, protective procedures, of the kind P1 through P3 which were earlier described, can we be fairly sure that the kind of antiseptic measures taken through those three stages are ones that would effectively kill any sort of organisms that might otherwise escape into the atmosphere that would have had these genetic changes, to which we might then be subject to illness?

Dr. SINGER. I think both Dr. Barkley and Dr. Curtiss have pointed out that theoretically, the mechanisms are very good but the problem is always that experiments can go wrong when people are involved.

So, while in an ideal situation one would say that the methods are good to such-and-such a probability, the real problem is to protect against accidents. This is why, with experiments deemed to be of greater possible risk, the containment procedures, both biological and physical, are increased in order to take account of the possibility of an accident.

But I don't think that anyone can say that any of them are absolutely perfect. I don't think that can be said.

Mr. KRUEGER. If I might, Mr. Chairman——

Chairman THORNTON. Please.

Mr. KRUEGER [continuing]. Proceed with one or two further questions.

First: I should direct this at least initially to Dr. Curtiss and then someone else might wish to comment. I'm wondering, when we use a sort of mechanism enfeebling *E. coli*, such as you describe, to what extent is the scientific research of others limited by dealing always with this kind of *E. coli*?

Dr. CURTISS. Well, maybe the best way to answer that question is by analogy. Shortly after the turn of the century, when the Wright brothers developed their first airplane, it was difficult to envision how that development would allow for the mass transit of human species wherever members of that species wanted to go. And with only a limited number of approved disabled *E. coli*'s, and plasmid, and bacterial vectors, the research is, to some extent, limited in its possibilities. Certainly, this would be more so if all recombinant research were required to use available EK2 systems.

I might add that some of these enfeebled systems behave very differently than EK1 *E. coli* cloning systems, and it has required that many microbiologists, geneticist, et cetera, who have worked with *E. coli* many years, learn a new bag of tricks, to make their experiments successful.

So, in a way, I think the use of these systems is tending to slow down research and from my own personal view this is not harmful. It is very important, however, that we eventually develop a greater diversity of such disabled host/vector systems to allow a greater diversity of experiments because the strains available may not facilitate or even allow the success of certain contemplated experiments. This is only going to be possible with time and further study.

Dr. WALD. The New York Times reported that there are 86 university laboratories getting into it at present; and at least 9 pharmaceutical companies.

Mr. KRUEGER. Eighty-six plus nine.

And of these two have P4 protection facilities? Is that correct?

Dr. WALD. No. Aren't the P4's just being built?

Dr. BARKLEY. There are no P4 facilities that are currently being used for recombinant DNA studies.

Mr. KRUEGER. I see.

Dr. BARKLEY. The NIH is currently rehabilitating four facilities that will be used to support such work. Two are located at the Cancer Research Center and two are located on the Bethesda campus of NIH.

There are two facilities that are currently operating in the United States at this time under conditions comparable to the P4 level. One is at the Center for Disease Control in which they are currently studying Lassa virus and Marburg virus; and the second is the Walter Reed facility at the Fort Detrick location, which is currently studying Machupo virus. All three of these viruses are classified by the Center for Disease Control as high-risk human pathogens.

Mr. KRUEGER. If these 86 plus 9 were to be required, for example, to adopt P4 kinds of protection facilities, what kind of costs are we talking about? That is my first question.

The second question would be, once the costs are themselves incurred, is the sheer process of going about the research made more difficult? In other words, I might feel safer crossing Independence Avenue if I wore, you know, a medieval coat of armor, but I might not necessarily wear that medieval coat of armor because it would make me miss too many votes because I'd get there too late, or something like that. And I'm wondering if this is a kind of medieval coat of armor which if we required it of all these laboratories, the rate at which they could carry out the research would be very much smaller and be more difficult.

Dr. WALD. Could I say something?

Chairman THORNTON. Dr. Wald.

Dr. WALD. At the end of my prepared remarks there is something that threatens the whole of American experimental science. It is that the common direction of the thoughts involving legislation in this regard—and, incidentally, everybody now concerned considers legislation to be inevitable—that the kinds of legislation that I hear being discussed, if that sort of thing is really instituted, I think scientists of every kind in this country haven't quite taken in what it will mean.

It will mean setting up a new bureaucracy for investigating, licensing, supervising, and controlling what goes on in research laboratories. First of all, one can foresee that once that happens it will stay with us, in all likelihood, indefinitely.

Mr. KRUEGER. Bureaucracy has a very long genetic life. [Laughter.]

Dr. WALD. Right.

And, second, it will by no means confine itself to recombinant DNA research. Its expansion to all other kinds of laboratory research has in fact been invited by proponents of gene splicing, who have repeatedly said that all exploration of the unknown is risky, all scientific research is dangerous. And if not challenged, this goes down very well.

Now, I have challenged it a few times by saying, "So far as I know I've never done a dangerous experiment in my life." And I've had the reply, "Oh, no? Don't you use alcohol for extractions? Isn't that inflammable?" Like the gas in everybody's automobile.

And you know I'm not seeing ghosts. We are already under the workers health and safety regulations, which industry fights off but which universities embrace. Why? You can get a new bureaucracy going in the university—and if you think bureaucracies just operate in government, just visit any present-day university. You'll really see some.

So, we've already had them coming down on us. I'm talking of my home institution, you know, Harvard. Where do you keep your alcohol? Where do you keep your petroleum ether, et cetera? You know.

The thought that all of that will shortly be regulated is very—you know, it's quite a possibility—and that would really get in the way, not only of the speed, but of the whole quality of experimental science in this country. I can hardly think of anything worse.

Now, that prospect can be met in one very simple way. I almost shudder to say it on this panel. That is by segregating this research above the P1 level, to a few national or regional laboratories, and then doing all the controlling internally, and leaving the rest of the scientific enterprise in this country unhampered.

Mr. KRUEGER. Dr. Curtiss?

Dr. CURTISS. I'll just make a few comments. Dr. Barkley may want to correct me on some of this.

It's my understanding that to construct and equip a good P4 laboratory, it would cost somewhere between $500 to $1,000 a square foot. The fact of the matter is if we had to design a P4 laboratory, I wouldn't; first, because I don't have $1 million and doubt that I could get it; and, second, I think that there's another major problem in continued escalation of required containment for certain recombinant research.

My own personal view at this moment in time is that the NIH guidelines have a good degree of conservatism in them. I didn't think that 3 years ago, but I've learned a lot since then, a lot of it based on experiments that we and others have done.

But there is a fear that I have that was discussed at the National Academy of Sciences forum workshop that I chaired, and that is the problem that arises by overkill. People in the scientific community who have been debating many of these issues, although there are exceptions, feel that the guidelines provide a good margin of safety, and if that margin of safety that is required gets to the point where the scientific community feels that it is an absurdity, or tendency to feel contempt for such requirements, it will be just like a law which nobody wants to obey.

I think that that's a real hazard, because the one thing that we certainly don't want to engender is contempt on the part of people, whether in this country or overseas, for the sorts of regulations that we are trying to evolve. The NIH guidelines are not perfect, but they make sure that we can proceed at a rather slow, reasonable pace, gathering more information about the potential risks.

And so to say that everything ought to be done in a P4 facility would have a negative result all the way around. A lot of scientists wouldn't do research, others might have the P4 facilities and then have a door going directly from their office into the lab, and just violate the whole principle of the facility.

Mr. KRUEGER. So, in summary then, from two different perspectives, we're hearing that to expect anything like P4 facilities for all of the places who would like to do this research would really be unreasonable, both in terms of scientific freedom and freedom of movement, and also in terms of cost.

And Dr. Wald suggested that it would be appropriate perhaps to restrict such research to specific institutions.

Dr. WALD. I was talking about P3.

Mr. KRUEGER. Oh. You——

Dr. WALD. I was talking about P3. I would assume these people don't really need P4.

Mr. KRUEGER. P4 is——

Dr. WALD. I would like to see the P2 restrictions jacked up to the P3 level. Also, from the beginning it has been my view, as that of Prof. Robert Sinsheimer at Cal Tech, that this work should be segregated outside of centers of population.

Mr. KRUEGER. So these——

Dr. WALD. Outside of crowded cities, and as far as I'm concerned, outside of universities. The trouble there, as I see all around me, is that the workers regularly go out of the laboratory to teach classes of young students. I think that is impermissible.

But it's P3 I was talking about segregating. And raising P2 to P3 so that is segregated too.

Mr. KRUEGER. Thank you for the clarification.

Finally, I wonder to what extent this kind of research is going on largely in the United States of America and to what extent it is spread across other countries, and whether they have substantially different precautions.

If this was covered when I was in another committee meeting, I apologize.

Chairman THORNTON. A very brief reference was made to research going on in seven countries. I think it might be useful to expand upon the policy considerations which they are undergoing.

Dr. SINGER. There is research going on in several countries in Western Europe, in the Soviet Union, in Japan, probably in Australia and Canada.

Three countries—the United States, Great Britain, and Canada—have separately evolved sets of guidelines. The guidelines are based on very similar principles in terms of assessing the risks of different experiments and also in establishing the principles of physical and biological containment, although the emphasis given to one or another differs from one set of guidelines to another.

In fact, if you look at the three sets of guidelines, they are very similar in the ranking of experiments according to risk and in terms of the containment requirements. They are not, however, identical.

It appears that in other countries there will not be independent attempts to devise sets of guidelines, that there will be a decision to use one or another of the existing sets of guidelines. And it isn't perfectly clear whether the British guidelines or the American guidelines will be adopted by one or another country at the present time.

The procedures for implementing the guidelines and for controlling work will differ substantially in other countries from the procedures

outlined in NIH guidelines. This primarily is a reflection of the smaller size of those countries and the smaller size of the relevant research community, so that it's possible to consider projects on a case-by-case basis by a central committee. It is much more difficult to do this in the United States given the bulk of the work that's going on.

There have been reports of experiments in the literature from various countries, and I think one can expect that there will be more and more of these in time.

In addition, there are efforts that we mentioned, basically by international organizations, to compare guidelines, give advice to people in different countries, disseminate information, sponsor training courses, and so forth. These organizations are both official governmental organizations, such as the WHO, and independent scientific organizations, such as the International Council of Scientific Unions and the European Molecular Biology Organization.

Mr. KRUEGER. Thank you very much.

And just as a final brief comment, I would simply observe that one of the things which we face here is the problem that, although it may be to the particular advantage of any individual scientist undertaking his or her research to try to proceed further and to push the frontiers a bit further, it is our responsibility not only to see that that scientist has the opportunity to carry out his research, but also that the public is protected at the same time.

I wish very much to thank the chairman and you for this excellent presentation. Thank you, Mr. Chairman.

Chairman THORNTON. Thank you, Mr. Krueger.

Mr. Hollenbeck, do you have any other questions?

Mr. HOLLENBECK. I would like the opportunity to submit some in writing.

Chairman THORNTON. I think I would like to ask each of the panelists if he or she would have objection to responding to such written questions as may be submitted for further clarification of the issues which have been presented today. I believe all are nodding affirmatively that they would be pleased to do so.

I want to thank each of you on the panel for your responsive and thoughtful testimony. I think it has been very helpful in focusing upon the issues which are presented.

Tomorrow we will be discussing in greater detail the potential risks and benefits of this kind of research and on Thursday we will deal perhaps a little more with questions regarding international research efforts.

Dr. Wald, I was very impressed with your suggestions that we need to be concerned about the operation of a kind of Gresham's law which might lead to the gravitation of DNA research to those countries or those areas which provide the least-effective guidelines or controls for that research.

And if there is a final question, that has occurred to me, it is this: Is this research not so terribly difficult as to be within the reach of knowledge of all college biologists? Could these individuals get some of the vectors and some of the chemicals which are necessary to split the genes

and cause perhaps less-well-controlled recombinations to occur in very rudimentary laboratory facilities?

Is that possible?

Dr. WALD. Well, now, I confidently expect this sort of thing to appear very shortly at high school science fairs.

Chairman THORNTON. This is what I've been told, that we're dealing with techniques which on a very rough and unguarded level can be accomplished in very limited laboratory facilities.

Am I getting an agreement generally across the board on that?

Dr. SINGER. I would say that it is relatively easy to sit down and try to plan the experiment. You come across certain barriers where certain kinds of equipment would be ideal to have. But I think one could make the attempt without it.

There are, however, other kinds of experiments that I've seen at high school science fairs that I think ought not to be done by high school students. And I might just tell you a very brief anecdote that happened to me this week. I have a 13-year-old daughter in the seventh grade who did a project in which she tried to isolate from tap water, milk, and air, the bacteria that would be resistant to penicillin. Therefore, she had plates with bacterial colonies growing on them.

This is not a dangerous experiment, and it failed because it's not very easy to isolate such resistant bacteria.

But she did have plates with organisms on them that were uncharacterized, and I said to her that I thought that she ought not to bring these into school for the science fair, that we ought to destroy them because they were uncharacterized organisms. We were able to take good care of them at home in the kitchen but they certainly shouldn't be taken to school and perhaps be opened up.

She was given a failing grade on her project because she didn't bring in the evidence that she'd actually done the experiment. And she's very angry with her mother. [Laughter.]

Chairman THORNTON. I want to thank you for sharing that with us.

I do appreciate so much the appearance of each of the members of this panel, and unless there are further questions from either members of the committee or staff, the hearing will be adjourned to meet again tomorrow morning at 9 a.m.

[The hearing in the above-entitled matter was adjourned at 12:30 p.m., to reconvene at 9 a.m., Wednesday, March 30, 1977.]

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

WEDNESDAY, MARCH 30, 1977

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY,
Washington, D.C.

The subcommittee met, pursuant to adjournment at 9:06 a.m., in room 2318, Rayburn House Office Building, Hon. Ray Thornton (chairman of the subcommittee) presiding.

Mr. THORNTON. The hearing will come to order.

We're starting some 30 minutes ahead of the usual scheduled time this morning in order to accommodate a meeting of the full Committee on Science and Technology at 11 o'clock.

We very much appreciate the early arrival of our distinguished group of witnesses this morning, Dr. Cape, Dr. Nathans, Dr. Signer, Dr. Cavalieri and Dr. Baltimore. We are looking forward to your testimony.

We have received prepared statements which as each of you give your presentation will be made a part of the record.

In order to afford an opportunity for discussion between the members of the panel who are testifying this morning and questions, I am going to ask that each of you make an effort to summarize your prepared statements, knowing that your statement will be made a part of the record. In suggesting that, I do not mean to suggest that you abbreviate it so much as to make it difficult to understand, because I think each of the other members here is going to want to be able to have an exchange of views.

Our first witness this morning is Dr. Ronald Cape, who is president of Cetus Corporation, and he'll be discussing the issue of the potential risks and benefits associated with recombinant DNA research. Our hearings today will center upon this question, an assessment of risks and benefits, and we are looking forward to the views of each of the witnesses. At this time I would like to recognize Dr. Cape.

[A biographical sketch of Dr. Cape follows:]

DR. RONALD E. CAPE

Ronald E. Cape, president of Cetus Corp., Berkeley, Calif. AB (chemistry), Princeton University 1953; M.B.A., Harvard University 1955; Ph. D. (biochemistry), McGill University 1967; post-doctoral fellowship, University of California, Berkeley, 1967–70—Molecular Biology and Virus Laboratory.

STATEMENT OF RONALD E. CAPE, PRESIDENT CETUS CORP., BERKELEY, CALIF.

Dr. CAPE. Thank you, Mr. Chairman.

I would just like to add a little personal background.

I suppose I'm identified here as an industry executive. Let me add that I'm also a molecular biologist, and my Ph. D. thesis was on "The Structure of DNA," and my post-doctoral work at Berkeley studied the genes responsible for DNA replication in a virus. But unlike all the other witnesses, I have not been a teacher, and I hope I can overcome that deficiency in presenting my views here.

The prospect of extensive academic and industrial research in the field of recombinant DNA has resulted in intensive public discussion. This hearing is a significant element in that discussion. It is now widely recognized that the profound nature of the technology raises equally profound questions as to its best possible applications, and indeed, the ultimate question as to whether, in fact, there is to be any application at all. There is the further question regardig how, in fact, these decisions are going to be made—an important public policy question that is by no means confined to the field of recombinant DNA.

In briefly addressing this latter point, I should state my belief that no one speaks for U.S. industry on this point. Perhaps I might even go so far as to say thank God no one speaks for the industrial establishment. There are differing views, and although I would hope that most reasonable executives would agree with what I say, I speak only for our company, Cetus Corp. However, I was personally present at the two meetings referred to by Professor Wald yesterday at which industry representatives met with Dr. Fredrickson at NIH last June and with Dr. Ancker-Johnson of the Department of Commerce last November. I do not agree with Dr. Wald's report or interpretation of what took place at either meeting, and my report is not hearsay. I would be happy to respond to any questions on that subject.

Mr. THORNTON. We will be very pleased to hear your assessment of that, and to develop a full presentation in order for the committee to make its review.

Dr. CAPE. I'll be glad to do so.

Industrial research has its risks and rewards, just as does academic research. It's not as romantic as academic research, and its risks and rewards are most frequently stated in financial terms. If we properly address a need, we'll make money—if the need is genuine and large, we'll make a great deal of money. If we guess wrong, we lose. Those are the rules, and we assume that most Americans are content with them.

So let me begin by stating that we welcome this public inquiry and involvement. We firmly believe that science is for the people, that in basic research, the assumption underlying governmental support is benefit to the people, and society wants a return on its investment. By the same token, we believe that the way our society is organized, implementation of discoveries commercialization, if you will, is the assigned task of industry. Where else will it be done? But we also recognize our responsibilities. So it's not a question of profits, no matter what, and it's certainly not a question of our strategy, no matter what.

These are not idle platitudes. Let me cite two examples: First, as we all know, the NIH Guidelines presently lack clout with any institution, group, or company not presently receiving NIH funds. Compliance with the guidelines will cost money, a lot of money, and it has to be spent now. Most of the more appealing commercial applications of recombinant DNA technology won't be profitable for many years to come. Yet it is true for us, and I hope for other companies, that there is utterly no intention of undertaking any work at all in this field except in full compliance with those guidelines.

Mr. Chairman, I would like to present an important clarification of a subject alluded to repeatedly in yesterday's testimony. The work at General Electric by Dr. Chakrabarty did involve some clever manipulations of plasmid in *pseudmonas* but it did not involve what we all agree is meant by recombinant DNA.

Further, many of us feel, apprehensive though we may be about bureaucracy, that Federal legislation closing that loophole is in the public interest, and very much to be desired. However, I would add that because I believe that there is no likelihood of hasty, inappropriate industrial activity, that such Federal legislation should not be precipitate. We feel that full public discussion should precede passage of any act. We support the legislation proposed in last week's report to HEW Secretary Califano by the Interagency Committee on Recombinant DNA Research, chaired by Dr. Fredrickson. If that report has not already been submitted for the record, I would like do so.

Mr. THORNTON. We'll be pleased to receive the report and to consider its inclusion in the printed record. We do not wish to duplicate printing of a report which is already widely available.

Dr. CAPE. The second observation regarding our public responsibilities concerns a popular misconception about our plans. We cannot, and we will not, make plans at the specific level, until the legislative and regulatory environment is clarified. We regard our possible avenues of behavior as being very dependent upon what makes sense after the public discussion has culminated, as we hope it will, in legislation which we will regard as a public conclusion. Then we hope it will be clear to us how to intelligently plan for the future.

Our hope is that it will be a very exciting future. The beneficial outcomes of this work fall into two categories: (1) Fundamental understanding of processes of life and disease, and (2) facilitation of heretofore impossible products and processes. I will dwell mainly on the latter. We are already making commitments in the hope that there will be many beneficial outcomes. This involves building teams, ordering equipment, and discussing many possible applications. As I said before, if we are wrong, and the work never gets started or successfully completed, we will have gambled and lost. But we will not gamble with issues of safety and prudence. We are not yet doing work with recombinant DNA. But we hope to. If it is accepted that in this field, as in other fields, the practical application is the role of industry, what sequence of events can we look to?

First, it is important to stage any proposed sequence of activity with several thoughts in mind.

(*a*) Safety: Looking ahead to any commercial application of recombinant DNA technology, we must be aware that production organisms

must be deemed safe under criteria analogous to those now applied to the biological containment parameters like EK2 and EK3 in the research context. Work must anticipate by years the ultimate need for production organisms which satisfy a rigorous set of standards. We can't tell today whether or not *E. coli* will ultimately be acceptable, no matter how crippled, and to this end work should begin soon to examine and prepare alternative organisms for commercial use. Dr. Curtiss yesterday called *E. coli* the workhorse of molecular genetics. We at Cetus Corp. propose to prepare an entire stable of such workhorse micro-organisms. I want to stress that such a program, which we are actively considering, does not, at first, require the kind of recombinant DNA experiments which led to the guidelines. What we're talking about is a large amount of pedestrian hard work in conventional microbial genetics.

(*b*) Economics: The ultimate commercial application of this technology will require a great deal of developmental work after most of the intellectual excitement has gone. By way of illustration, I believe that the demonstration of the production of human insulin in *E. coli* in a test tube will occur sooner than many think, but that it will be many years and many millions of dollars more before we see a production plant which utilizes a new, safer organism, to efficiently make large quantities of insulin at a price which makes sense.

(*c*) Choice of protein: Most simply stated, recombinant DNA technology merely makes possible the manufacture, in a convenient cell, of a protein or proteins, whose blueprint, or DNA, comes from another, unrelated cell. The most dramatic illustrations of this possibility usually deal with things which are most far out, and on which the worst fears are also able to fasten. Thus, it is very exciting to talk of treating disease quickly, cheaply, very effectively, and possibly very safely with human proteins which we call antibodies. It is very exciting to talk of the advantages of antibodies over antibiotics—antibodies may be safer, and they may be effective against viruses and maybe even cancer cells, which antibiotics, essentially, do not attack. But the fact is that such an application is very many years away, will cost a great deal of money to reduce to practice, and involves some experiments which most experts, including proponents of this work, acknowledge to be in the higher risk category. And in this, as in many other exciting applications, there are a host of problems to be overcome, and many questions to be asked, any of which may render the project unsuitable. The groundwork should be laid now in order to enable at least some of these revolutionary beneficial outcomes to materialize in the 1990's. This groundwork should address questions of risk. These questions cannot be resolved in learned debate—they must be addressed experimentally. It is welcome news that NIH is now ready to do some of this experimental probing.

Thus, the long-range programs cannot be identified with precision for sometime yet. But unless some work begins soon to answer some of these real questions, the ultimate benefit will be even farther away. The time frames are long as it is. Each participant, each company, must make its own assessment. But one thing is clear to me: There is no place in this field for any company with only short-range thinking or objectives. Profits are not around the corner.

There are, however, some less long-range programs—less likely to create newspaper headlines, less likely perhaps to alarm critics of this work, but very likely to provide benefit in today's world of industrial fermentation—which gives us antibiotics, beer, cheese, and a host of industrial chemicals. By and large, we have historically accepted that a new compound discovered in a particular organism must be produced commercially in that organism. If penicillin is discovered in the mold penicillium, then that's the organism we're stuck with for commercial production. Recombinant DNA technology renders it possible to move these capabilities into safer and more economical production organisms. This is particularly important today when microbial processes could in many cases produce chemicals which today must be made from petroleum sources. Even now, some microbial processes, if more efficient, could further reduce our dependence on foreign oil.

It is to these applications, far removed, we think, from the glamour and from the public concern with manipulation of the genes of viruses and humans, that the first industrial attention should be directed. We hope to do so.

Mr. Chairman, we've been asked to comment on patent questions. It is our belief—and I'm speaking only for our company here—that the only changes desirable in present patent laws would be those which would remove the catch-22 dilemma confronting those who wish to patent developments in this field. It is my understanding that at present there is some learned opinion that compliance with the NIH guidelines constitutes publication, which very act of publication precludes ever-receiving patent protection. That's a "no win" situation, Mr. Chairman. As a separate subject, in the patent area, if—I say "if"—it is deemed to be in the public interest to grant accelerated treatment to patent applications so that whatever secrets are contained in these applications could be made public as quickly as possible, that's fine. But we do not agree with any use of accelerated patent processing as an inducement to anyone to comply with any regulations or guidelines. I'll repeat—such compliance should be the subject of legislation, and we support the Interagency Committee's suggestions.

I don't wish to take up the subcommittee's time reciting again the litany of benefits and risks attendant on work in this field. The December 1976 Supplemental Report II prepared for this committee deals fully and very well with these issues. I would like to make several brief points, however, and then I'll close.

My brief points are:

First. The assessment of unknown risks compared to benefits, some of which are certain and some of which are freshly speculative, cannot be made by debate. Methodologies must be developed to evaluate both experimentally. The categorization of risks and the absolute prohibition of certain experiments and the assignment of biological and physical containment levels deemed appropriate to various kinds of experiments is wise. Let's be sure, however, to regard the process as one of genuine feedback. The guidelines are today's perception of where prudence lies. Many experiments should be designed, and the results of these experiments should be used, to consider changes in the guidelines, in either direction, as the facts dictate. Who is to make the determinations, and with what balanced input remains to be estab-

lished. Hopefully the Secretary of HEW will have an appropriate basis for such determinations down the road.

Second. Let's not mix apples and oranges. Let's not rush recklessly ahead, but let's not, on the other hand, fail to move forward because of a fear that we are opening a Pandora's box, or that no real need exists and that this work is not worthy of a high priority in this society. If it is a Pandora's box, it's already opened. But Dr. Wald was absolutely right in maintaining that regardless of what goes on elsewhere we must set an example. The whole world is watching. We have confidence that this society can handle its alternatives and deal with its responsibilities as they arise. Moving new genes into bacteria is no more related to diabolical genetic manipulation of human beings than is the breeding of cattle or corn.

Let's by all means prohibit the diabolical, or anything that leads to it. We have seen significant advances in recent perceptions and legislation regarding experimentation on human subjects. Let's continue that dialog. But it's not simple. For example, when you approve wide use of a new vaccine, you are profoundly and intentionally intervening with evolution of viruses that work within human cells and interact with human DNA in ways not yet fully understood. Let's not fail to increase that understanding, while at the same time addressing the equally important social consequences. But let's not make recombinant DNA research, or U.S. industry, which actually is doing practically none of it right now, a whipping boy for social problems that have nothing to do with the specific and very important question of science policy, which this subcommittee is very properly examining here today.

Thank you.

Mr. THORNTON. Thank you very much, Dr. Cape.

[Dr. Cape's additional submissions for the record are as follows:]

February 11, 1977

Dr. John F. Finklea, Director
National Institute for Occupational Safety and Health
5600 Fishers Lane
Rockville, MD 20852

Dear Dr. Finklea:

Thank you for requesting our comments and proposals in your letter of December 27, 1976.

I am very sorry that I've been almost constantly away from my desk since December 18. When you called I had just returned from Germany, and I must apologize for the delay in responding to your very welcome request for comment. I reiterate this apology because, as I have written to Dr. Fredrickson, we eagerly look forward to all opportunities to interact with responsible authorities in this field.

Cetus Corporation is currently planning and organizing a recombinant molecule research facility for the purpose of exploring the applicability of this new technology to industrially relevant projects. We feel establishment of guidelines and suggested procedures relating to occupational safety, health surveillance and control measures would be most useful.

We agree with the establishment of a central registry.

We agree that a program of medical examination of recombinant DNA research investigators and personnel prior to initiating this type of research and periodically thereafter is a sound idea.

Some issues come to mind. What specifically would a consulting physician be looking for and what types of records should be kept? Clearly, adequate labeling and posting should be a mandatory requirement (as in radioisotope work). Similarly, segregation of facilities (already in the guidelines for P2, P3, and P4 work) may be useful for preventing inadvertent cross-contamination, etc. It is not clear what type of general area monitoring and routine screening procedures are applicable to recombinant DNA research. The services and measures already in existence for investigators working with radioisotopes (area monitors, film badge and TLD dosimetry ring services, blood and/or urine analysis) or specific viruses (serum samples and antibody testing) do not readily lend themselves to routine, general survey procedures for a variety of microorganisms that may contain recombinant DNA. While the use of genetically marked strains (e.g. X1776) certainly facilitates the detection of contaminant microorganisms within a transformed microbial population, it must be determined how one can routinely monitor exposure to recombinant DNA in unspecified microorganisms, particularly if one is using complementation of an auxotrophic mutation rather than antibiotic resistance as the selective marker in the cloning vehicle.

Cetus Corporation, 600 Bancroft Way, Berkeley, California 94710 Phone (415) 549-3300

To properly design the record keeping so that it serves a useful future function, we would further urge that consideration be given to performing similar tests in a similar way for a similar time period on appropriate control groups.

Furthermore, it would seem to be important to have health records of people in an industry that go back before the time that there is wide use of recombinant DNA technology within it. This is a situation that is likely to change quite quickly from time to time. Also, to provide a calibration as to *relative* hazard, thought should be given to studying, in parallel, other potential sources of microbial infection, both in institutional and industrial settings.

We feel that thorough training and scrupulous microbiological technique in conjunction with appropriate physical and biological containment procedures are vital. We would endorse a training program along the lines of the University of Minnesota - N.C.I. Office of Research Safety course we recently attended at Stanford University. While that course was very helpful, we feel a training program specifically directed toward work with DNA and microorganisms (rather than attempting to adapt the cell and virus training course) and focusing on problems specifically related to bacteria and fungi would be enthusiastically supported by both the academic and industrial communities. This training program could take the form of a short course (3-4 days in length) that would be given several times a year in different parts of the country, and could be updated and expanded by supplemental information being published in the N.A.R.S.M. communication series. (The contribution from Dr. Ann Skalka's laboratory in the recent N.A.R.S.M. communication, for example, discussed several detergents and disinfectants and conditions for inactivating not only microbial cells but also free DNA and bacteriophage populations.)

We hope these comments may prove useful. We earnestly request that when you have prepared a draft of any guidelines or regulations that will apply to industrial research, or any revisions of the existing guidelines that relate to safety and/or occupational hazards, we be permitted to comment and offer additional suggestions.

Once again, I'm sorry that my traveling activities prevented an earlier reply.

Sincerely,

CETUS CORPORATION

Ronald E. Cape, Ph.D.
President

REC/asg

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL
SAFETY AND HEALTH
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20852

December 27, 1976

Mr. Ronald Cape
President
Cetus Corporation
600 Bancroft Way
Berkeley, California 94710

Dear Mr. Cape:

The Secretary of HEW has asked Dr. Fredrickson of the National Institutes of Health (NIH) to chair an Interagency Committee on Recombinant DNA Research. Governmental agencies, universities and industries in this country and abroad are interested in recombinant DNA research techniques. NIH has developed and published in the Federal Register (Volume 41, No. 176, Thursday, September 9, 1976, page 38426 through 38444) a Draft Environmental Impact Statement entitled Recombinant DNA Research. It is my understanding that the Congress of the United States will be closely examining the findings of the Interagency Committee during its next session.

The Recombinant DNA Research Guidelines developed by NIH did not address potential occupational safety and health problems. We hope that the revised guidelines will provide more attention to workplace health and safety issues in laboratories in which recombinant DNA research would be performed. In many cases the involved laboratories are already covered by the Consensus Standards promulgated under the Occupational Safety and Health Act. One exception would be research undertaken in public universities in States not having State occupational safety and health plans that provide coverage for public workers.

Our Institute feels that revised Guidelines should provide for the establishment of a central registry of all workers engaged in recombinant DNA research or the operation and maintenance of laboratories and pilot plants where recombinant DNA research is carried out. We believe that there should be provision for a program of medical examinations for such workers prior to placement and periodically thereafter. We believe that all workers should be adequately informed about potential health risks associated with recombinant DNA research and that there should be adequate labeling and posting in each work area. Because our concern about diseases with a long latency period,

we believe that there should be provision to retain all health records and all records detailing the configuration and operational history of each research facility for 30 years. Some provision to facilitate medical follow up of such workers is needed. There should be medical reporting of all illnesses, injuries and deaths among all workers engaged or formerly engaged in recombinant DNA research.

We feel that it would be useful to develop appropriate environmental and workplace monitoring systems to assure that inadvertent exposures to recombinant DNA organisms are not taking place. One should also develop adequate workmen's compensation provisions to insure against occupational related injury and illness among recombinant DNA research workers.

I would appreciate your helping our Institute deal with occupational safety and health issues evolving from the recombinant DNA research. Has your company planned or initiated recombinant DNA research? If recombinant DNA research is contemplated by your company, what occupational safety and health surveillance and control measures will you advise? Have you discussed the recombinant DNA research issue with worker representatives, union health and safety officials or health and safety committees in your plants? If you think specific research or policy studies dealing with the recombinant DNA issue should be carried out by our Institute, please describe these studies in a brief paragraph.

I would be most happy to receive any other comments you may wish to forward on the recombinant DNA issue or any other occupational safety and health issues and would be glad to discuss the recombinant DNA issue with you if you so desire.

Sincerely yours,

John F. Finklea, M.D.
Director

March 11, 1977

The Honorable Jacob K. Javits and
the Honorable Edward M. Kennedy
United States Senate
Washington, D.C. 20510

Dear Senators Javits and Kennedy:

Thank you for your letter of February 14, 1977.

1. Catus Corporation is not engaged in, nor has it been engaged in the conduct of recombinant DNA research anywhere.

2. We do, however, share the excitement of others regarding the potential benefits of knowledge and possible practical applications of this technology. We hope that it will be practical and generally acceptable that private companies participate in this adventure, and if so we very much intend to be counted among them. Sufficiently so, that we are presently hiring staff and planning potential projects. No final decisions have been made as to the precise nature of these projects, nor will they be made before this public discussion has resulted in clarification. However, we will certainly begin with experiments generally considered to be of very low risk or of no risk whatsoever.

3. We are indeed willing to register and have already publicly expressed full willingness and intention to comply with the NIH guidelines. We welcome this opportunity to reiterate that intention.

4. We can comply; we suggest no guideline changes at present.

5. Our company has not obtained any patents for recombinant DNA research.

Gentlemen, I would like to take this opportunity to ask for your help in connection with one major difficulty. We very much wish to participate in this important dialog. It is, however, not clear who speaks for the government, who speaks for the "public," and it is clear that no one can, or indeed should presume to

speak for "industry." Nor, unilaterally, does anyone speak for "scientists." This fragmentation has not helped clarification or study of the issues, and we are frustrated by the lack of a universally recognized forum for this very important public discussion. Could there be a legislative answer?

Yours sincerely,

CETUS CORPORATION

Ronald E. Cape, Ph.D.
President

REC/asg

United States Senate

WASHINGTON, D.C. 20510

February 14, 1977

Dr. Ronald Cape, President
Cetus Corporation
600 Bancroft Way
Berkeley, California

Dear Dr. Cape:

As you know, the conduct of recombinant DNA research has become the subject of increasing debate and concern both within the scientific community and more recently, in public forums. The Subcommittee on Health has maintained an intense interest in the issues which have prompted the controversy over such research and has held two public hearings concerning these issues over the past two years.

At the last hearing on September 22, 1976, the Director of the National Institute of Health, the Assistant Administrator for Research and Development of the Environmental Protection Agency, a panel of eminent scientists, and the President of the Pharmaceutical Manufacturers Association, provided thoughtful testimony concerning the status of recombinant DNA research and the guidelines recently promulgated by the National Institute of Health for the conduct of such research. As expressed by the Director of NIH, the object of the guidelines is to minimize the associated risks while permitting appropriate types of this research to continue with its great potential benefit to mankind.

The NIH guidelines are now being adopted by all federal agencies conducting or supporting such research. Mr. Joseph Stetler, the President of the Pharmaceutical Manufacturers Association stated at the subcommittee hearing that pharmaceutical companies intended to conform with the NIH guidelines and that the PMA would continue to work closely with NIH to work out minor problems so that compliance could be achieved.

It was the consensus of the witnesses before the subcommittee that the NIH guidelines should be extended to all sectors of the research community conducting recombinant DNA research, including the private sector and the international community. The subcommittee shares this view.

We wrote to President Ford on July 19, 1976, pointing out the necessity for such an extension and urging exploration of the means of implementation, including suggested legislation if necessary. President Ford's reply of September 22, 1976, indicated that the Interagency Committee on Recombinant DNA Research would be formed to review the activities of all government agencies performing or supporting such research and to coordinate activities with non-federal institutions. The first meeting of the Interagency Committee was held on November 4, 1976 and there have been several subsequent meetings. The Committee has discussed, among other things, the need to establish a central registry of all recombinant DNA research and existing legislative authority for regulation of such research.

In anticipation of the possible need for additional legislation to implement such registration and regulation, I would appreciate it if you would furnish the following information by March 15, 1977.

1. Is your company or institution engaged, or has it previously been engaged, in the conduct or support of recombinant DNA research in the United States or elsewhere? If so, please provide information concerning the nature and location of such research and identity of the company or institution conducting such research. Also please furnish the same information about any contemplated research of this kind.

2. If your company or institution has not engaged in recombinant DNA research, is such research being contemplated? If so, please provide the nature and location of such research and the identity of the company or institution which will conduct the research.

3. If recombinant DNA research is being conducted or contemplated, is your company or institution willing to register such research and comply with the NIH guidelines?

4. If your company or institution can not comply with the NIH guidelines, what changes in the guidelines would you suggest to make compliance possible?

5. Has your company or institution obtained any patents for recombinant DNA? If so, please furnish information concerning the nature of the patents and the dates they were issued.

Your cooperation in this important matter will be very much appreciated.

Sincerely,

Jacob K. Javits

Edward M. Kennedy

September 28, 1976

Dr. Donald S. Fredrickson
Director
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

Thank you for requesting our views on the question of patent applications in the area of recombinant DNA research activity.

We feel that there are two quite distinct reasons why this matter deserves the careful attention which you are giving it.

First, the profound and far-reaching nature of the patent claims, as we understand them, are such that should the patent be granted and be found valid, it seems that *any* application of recombinant DNA technology *in the United States* will require a license. There are serious questions respecting both the fairness and practicability of implementation of this kind of control. There are also public interest issues regarding the policing of this work in the United States and the effect which the limitation of at least the existing, far-reaching patent to the United States would have, encouraging nonlicensees to practise the inventions outside the United States.

The other major issue, again primarily one of public interest, concerns the environmental and other safety issues addressed by the recently published guidelines and the extent to which the way in which the patents are handled impinges on developments in this area.

Let us state our conclusions and follow them with some paragraphs of explanation.

> We feel that alternative 4 on page 3 of your letter is the most sensible way to proceed with two very important stipulations. First, we believe that any exclusive license, granted to anyone on any specific application of this technology, no matter how narrowly defined, and no matter for how short a period of time, would be extremely unwise. Secondly, using compliance with the NIH guidelines as a condition for licensing is a splendid idea, but the specific way in which this is implemented could be either the best or the worst feature of the program. We feel that the special needs of industry, which have not yet been properly considered* must be addressed in a fair and deliberate manner because it is from industry that the license fees are expected to come. We also have some concern about the nature of the enforcement of this compliance. Surely the universities are not set up to do this properly.

* Our strong views on this subject have already been communicated to you.

In short, Cetus Corporation intends to be active in this area and is willing to pay fair license fees, on an equal basis with others, on commercial applications. We would vigorously oppose the granting to anyone of an exclusive license of any sort whatsoever.

We have previously stated that we endorse and applaud the NIH guidelines, and that we have specific ideas about appropriate, somewhat different guidelines for industrial research and commercial application. Regardless of what decisions are made with respect to the patents, the public interest requires that these decisions be made openly in some process as yet to be defined.

Now to our reasoning. Probably, you have heard, as have we, that many scientists feel that there is a significant difference between the all-encompassing nature of the Stanford/UCSF patent and the University of Alabama patent. The latter, as we understand it, is much more in the way of an application generated in response to the first discovery. There will undoubtedly be many such derivative applications. It is the feeling of many that it is inappropriate to attempt to patent something as fundamental as a way of making recombinant DNA molecules. This is clearly something for the patent office, not for us, to decide. In this case, where the patent is restricted to the United States, the response to its broadness may consist of attempts to circumvent it. Particularly, if *exclusive* licenses are granted, those not licensed may feel that they have little choice but to look to remedies such as practising the invention outside the United States. That is not in the interests of the United States. Far better, we feel, to have it clear that HEW and Stanford University and UCSF have made an investment and facilitated an unprecedented scientific breakthrough for which they are entitled to a reward, and that nonexclusive fees are a fair and equitable vehicle for such reward. In the past exclusive licenses may have been seen as the only way to motivate industry to make the necessary investment to develop an invention to the point where there would be something to exploit commercially. This is clearly not the case here. Many companies have already asserted their intention to become involved in the field - it is difficult to understand how any significant biologically-based company could do otherwise.

But this brings us to the second major issue, and that involves safety and the public interest. As I stated in my previous letter to you, dated July 29, it is vitally important that the industrial community be imbued with the same concerns and awareness that prompted the academic community to begin the process which resulted in the promulgation of the NIH guidelines. Prudence, restraint, and sophisticated scientific judgment have to be combined in the determination of what work shall be done, in what sequence, and at what rate. The very nature of an exclusive license and particularly one with a short time limit, would encourage speed at the expense of the prudence which in the

public interest is now paramount. The way in which the licensing is implemented, therefore, must encourage this prudence in every possible way. Open licensing is one such way. Careful consultation with industry prior to announcement of any particular guidelines is another way.

It is our feeling that the practise of these inventions in the United States is likely to be more stringent and proper than elsewhere. This will serve no useful purpose if the corollary is that most of such work is therefore done *outside* the United States.

Another distinction which must be clarified arises from the second paragraph in the public relations release attached to your letter. It is said that the patent would cover commercial use of the process, but not academic or industrial research. I think it's clear that some of the nightmares which the guidelines are intended to obviate, if they were in fact to happen, could just as easily happen in industrial research (not covered by the patent) as in subsequent "commercial use." In fact, one could even surmise that the commercial use would be safer having been extensively tested during the period of industrial research for safety, among other parameters. How does one intend to police this industrial research? Could one circumvent the patent by conducting the industrial research (not covered) in the United States and then implement the commercial use in some other country? A not very difficult scenario for a multinational corporation!

So there are certainly some very loose ends and it is probably unreasonable to expect the granting of a patent to tie them up. It is even more unrealistic to justify the patent as a *means* of tying them up.

We feel quite differently about subsequent patents of a narrower nature, of which we believe the University of Alabama patent to be an example. Whether or not it is, one last point comes to mind. One can anticipate that a category of patents which would issue from this work would address the specific industrial processes (such as those mentioned in the press release to produce insulin and other hormones) made possible by the development of "new" bacteria. This is the real commercial payoff, the objective of the industrial research. As is the case with current microorganism strain development and selection programs in the antibiotics industry, the companies can be expected to jealously guard their unique microorganisms as being integral to the patented commercial process. The nature of recombinant DNA research means that these microorganisms will also have to be vehicles of an EK2 or more stringent type. The present guidelines insist upon the free availability of all such vehicles within the scientific community. It is unlikely that industry will want to invest much money and many years toward the development of such microorganisms if they are required to make the end result of all this work freely available.

We have probably only scratched the surface. We are carefully studying a wide variety of possible commercial applications of recombinant DNA technology and it is clear to us that large scale profitable industrial use is many years

away. This stems largely from our awareness of the public interest considerations. This does not mean that work cannot begin immediately. In fact, it must if those applications are to materialize in our lifetimes.

In this connection we want to reiterate our position. If a valid patent is awarded to Stanford University and the University of California, San Francisco, we will apply for licenses to practise those inventions. We favor the administration of such patents in conjunction with the Department of Health, Education, and Welfare as outlined in your alternative 4. And we urge that a great deal of careful study, soliciting many inputs, precede any final determination of any guidelines for recombinant DNA research by industry in the United States.

Yours sincerely,

CETUS CORPORATION

Ronald E. Cape, Ph.D.
President

REC/lmb

cc: Dr. Stanley Cohen
Dr. Carl Djerassi
Dr. Joshua Lederberg
Mr. Julian Stern
Dr. Julius Tabin

Recombinant DNA: Fact and Fiction

Stanley N. Cohen

Almost 3 years ago, I joined with a group of scientific colleagues in publicly calling attention to possible biohazards of certain kinds of experiments that could be carried out with newly developed techniques for the propagation of genes from diverse sources in bacteria (*1*). Because of the newness and relative simplicity of these techniques (*2*), we were concerned that experiments involving certain genetic combinations that seemed to us to be hazardous might be performed before adequate consideration had been given to the potential dangers. Contrary to what was believed by many observers, our concerns pertained to a few very specific types of experiments that could be carried out with the new techniques, not to the techniques themselves.

Guidelines have long been available to protect laboratory workers and the general public against known hazards associated with the handling of certain chemicals, radioisotopes, and pathogenic microorganisms; but because of the newness of recombinant DNA techniques, no guidelines were yet available for this research. My colleagues and I wanted to be sure that these new techniques would not be used, for example, for the construction of streptococci or pneumococci resistant to penicillin, or for the creation of *Escherichia coli* capable of synthesizing botulinum toxin or diphtheria toxin. We asked that these experiments not be done, and also called for deferral of construction of bacterial recombinants containing tumor virus genes until the implications of such experiments could be given further consideration.

During the past 2 years, much fiction has been written about "recombinant DNA research." What began as an act of responsibility by scientists, including a number of those involved in the development of the new techniques, has become the breeding ground for a horde of publicists—most poorly informed, some well-meaning, some self-serving. In this article I attempt to inject some relevant facts into the extensive public discussion of recombinant DNA research.

The author is a molecular geneticist and Professor of Medicine at the Stanford University School of Medicine, Stanford, California 94305. This article is adapted from a statement prepared for a meeting of the Committee on Environmental Health of the California Medical Association, 18 November 1976.

Some Basic Information

Recombinant DNA research is not a single entity, but rather it is a group of techniques that can be used for a wide variety of experiments. Much confusion has resulted from a lack of understanding of this point by many who have written about the subject. Recombinant DNA techniques, like chemicals on a shelf, are neither good nor bad per se. Certain experiments that can be done with these techniques are likely to be hazardous (just as certain experiments done with combinations of chemicals taken from the shelf will be hazardous), and there is universal agreement that such recombinant DNA experiments should not be done. Other experiments in which the very same techniques are used—such as taking apart a DNA molecule and putting segments of it back together again—are without conceivable hazard, and anyone who has looked into the matter has concluded that these experiments can be done without concern.

Then, there is the area "in between." For many experiments, there is no evidence of biohazard, but there is also no certainty that there is not a hazard. For these experiments, guidelines have been developed in an attempt to match a level of containment with a degree of hypothetical risk. Perhaps the single point that has been most misunderstood in the controversy about recombinant DNA research, is that discussion of "risk" in the middle category of experiments relates entirely to hypothetical and speculative possibilities, not expected consequences or even phenomena that seem likely to occur on the basis of what is known. Unfortunately, much of the speculation has been interpreted as fact.

There is nothing novel about the principle of matching a level of containment with the level of anticipated hazard; the containment procedures used for pathogenic bacteria, toxic substances, and radioisotopes attempt to do this. However, the containment measures used in these areas address themselves only to known hazards and do not attempt to protect against the unknown. If the same principle of protecting only against known or expected hazards were followed in recombinant DNA research, there would be no containment whatsoever except for a very few experiments. In this instance, we are asking not only that there be no evidence of hazard, but that there be positive evidence that there is no hazard. In developing guidelines for recombinant DNA research, we have attempted to take precautionary steps to protect ourselves against hazards that are not known to exist—and this unprecedented act of caution is so novel that it has been widely misinterpreted as implying the imminence or at least the likelihood of danger.

Much has been made of the fact that, even if a particular recombinant DNA molecule shows no evidence of being hazardous at the present time, we are unable to say for certain that it will not devastate our planet some years hence. Of course this view is correct; similarly, we are unable to say for certain that the vaccines we are administering to millions of children do not contain agents that will produce contagious cancer some years hence, we are unable to say for certain that a virulent virus will not be brought to the United States next winter by a traveler from abroad, causing a nationwide fatal epidemic of a hitherto unknown disease—and we are unable to say for certain that novel hybrid plants being bred around the world will not suddenly become weeds that will overcome our major food crops and cause worldwide famine.

The statement that potential hazards could result from certain experiments involving recombinant DNA techniques is akin to the statement that a vaccine injected today into millions of people *could* lead to infectious cancer in 20 years, a pandemic caused by a traveler-borne virus *could* devastate the United States, or a new plant species *could* uncontrollably destroy the world's food supply. We have no reason to expect that any of these things will happen, but we are unable to say for certain that they will not happen. Similarly, we are unable to guarantee that any of man's efforts to influence the earth's weather, explore space, modify crops, or cure disease will not carry with them the seeds for the ultimate destruction of civilization. Can

we in fact point to one major area of human activity where one can say *for certain* that there is zero risk? Potentially, we could respond to such risks by taking measures such as prohibiting foreign travel to reduce the hazard of deadly virus importation and stopping experimentation with hybrid plants. It is possible to develop plausible "scare scenarios" involving virtually any activity or process, and these would have as much (or as little) basis in fact as most of the scenarios involving recombinant DNA. But we must distinguish fear of the unknown from fear that has some basis in fact; this appears to be the crux of the controversy surrounding recombinant DNA.

Unfortunately, the public has been led to believe that the biohazards described in various scenarios are likely or probable outcomes of recombinant DNA research. "If the scientists themselves are concerned enough to raise the issue," goes the fiction, "the problem is probably much worse than anyone will admit." However, the simple fact is that there is no evidence that a bacterium carrying any recombinant DNA molecule poses a hazard beyond the hazard that can be anticipated from the known properties of the components of the recombinant. And experiments involving genes that produce toxic substances or pose other known hazards are prohibited.

Freedom of Scientific Inquiry

This issue has been raised repeatedly during discussions of recombinant DNA research. "The time has come," the critics charge, "for scientists to abandon their long-held belief that they should be free to pursue the acquisition of new knowledge regardless of the consequences." The fact is that no one has proposed that freedom of inquiry should extend to scientific experiments that endanger public safety. Yet, "freedom of scientific inquiry" is repeatedly raised as a straw-man issue by critics who imply that somewhere there are those who argue that there should be no restraint whatsoever on research.

Instead, the history of this issue is one of self-imposed restraint by scientists from the very start. The scientific group that first raised the question of possible hazard in some kinds of recombinant DNA experiments included most of the scientists involved in the development of the techniques—and their concern was made public so that other investigators who might not have adequately considered the possibility of hazard could exercise appropriate restraint. While most scientists would defend their right to freedom of scientific thought and discourse, I do not know of anyone who has proposed that scientists should be free to do whatever experiments they choose regardless of the consequences.

Interference with "Evolutionary Wisdom"

Some critics of recombinant DNA research ask us to believe that the process of evolution of plants, animals, and microbes has remained delicately controlled for millions of years, and that the construction of recombinant DNA molecules now threatens the master plan of evolution. Such thinking, which requires a belief that nature is endowed with wisdom, intent, and foresight, is alien to most post-Darwinian biologists (*3*). Moreover, there is no evidence that the evolutionary process is delicately controlled by nature. To the contrary, man has long ago modified the process of evolution, and biological evolution continues to be influenced by man. Primitive man's domestication of animals and cultivation of crops provided an "unnatural" advantage to certain biological species and a consequent perturbation of evolution. The later creation by man of hybrid plants and animals has resulted in the propagation of new genetic combinations that are not the products of natural evolution. In the microbiological world, the use of antimicrobial agents to treat bacterial infections and the advent of mass immunization programs against viral disease has made untenable the thesis of delicate evolutionary control.

A recent letter (*4*) that has been widely quoted by critics of recombinant DNA research asks, "Have we the right to counteract irreversibly the evolutionary wisdom of millions of years . . .?" It is this so-called evolutionary wisdom that gave us the gene combinations for bubonic plague, smallpox, yellow fever, typhoid, polio, diabetes, and cancer. It is this wisdom that continues to give us uncontrollable diseases such as Lassa fever, Marburg virus, and very recently the Marburg-related hemorrhagic fever virus, which has resulted in nearly 100 percent mortality in infected individuals in Zaire and the Sudan. The acquisition and use of all biological and medical knowledge constitutes an intentional and continuing assault on evolutionary wisdom. Is this the "warfare against nature" that some critics fear from recombinant DNA?

How About the Benefits?

For all but a very few experiments, the risks of recombinant DNA research are speculative. Are the benefits equally speculative or is there some factual basis for expecting that benefits will occur from this technique? I believe that the anticipation of benefits has a substantial basis in fact, and that the benefits fall into two principal categories: (i) advancement of fundamental scientific and medical knowledge, and (ii) possible practical applications.

In the short space of 3½ years, the use of the recombinant DNA technology has already been of major importance in the advancement of fundamental knowledge. We need to understand the structure and function of genes, and this methodology provides a way to isolate large quantities of specific segments of DNA in pure form. For example, recombinant DNA methodology has provided us with much information about the structure of plasmids that cause antibiotic resistance in bacteria, and has given us insights into how these elements propagate themselves, how they evolve, and how their genes are regulated. In the past, our inability to isolate specific genetic regions of the chromosomes of higher organisms has limited our understanding of the genes of complex cells. Now use of recombinant DNA techniques has provided knowledge about how genes are organized into chromosomes and how gene expression is controlled. With such knowledge we can begin to learn how defects in the structure of such genes alter their function.

On a more practical level, recombinant DNA techniques potentially permit the construction of bacterial strains that can produce biologically important substances such as antibodies and hormones. Although the full expression of higher organism DNA that is necessary to accomplish such production has not yet been achieved in bacteria, the steps that need to be taken to reach this goal are defined, and we can reasonably expect that the introduction of appropriate "start" and "stop" control signals into recombinant DNA molecules will enable the expression of animal cell genes. On an even shorter time scale, we can expect recombinant DNA techniques to revolutionize the production of antibiotics, vitamins, and medically and industrially useful chemicals by eliminating the need to grow and process the often exotic bacterial and fungal strains currently used as sources for such agents. We can anticipate the construction of modified antimicrobial agents that are

not destroyed by the antibiotic inactivating enzymes responsible for drug resistance in bacteria.

In the area of vaccine production, we can anticipate the construction of specific bacterial strains able to produce desired antigenic products, eliminating the present need for immunization with killed or attenuated specimens of disease-causing viruses.

One practical application of recombinant DNA technology in the area of vaccine production is already close to being realized. An *E. coli* plasmid coding for an enteric toxin fatal to livestock has been taken apart, and the toxin gene has been separated from the remainder of the plasmid. The next step is to cut away a small segment of the toxin-producing gene so that the substance produced by the resulting gene in *E. coli* will not have toxic properties but will be immunologically active in stimulating antibody production.

Other benefits from recombinant DNA research in the areas of food and energy production are more speculative. However, even in these areas there is a scientific basis for expecting that the benefits will someday be realized. The limited availability of fertilizers and the potential hazards associated with excessive use of nitrogen fertilizers now limits the yields of grain and other crops, but agricultural experts suggest that transplantation of the nitrogenase system from the chromosomes of certain bacteria into plants or into other bacteria that live symbiotically with food crop plants may eliminate the need for fertilizers. For many years, scientists have modified the heredity of plants by comparatively primitive techniques. Now there is a means of doing this with greater precision than has been possible previously.

Certain algae are known to produce hydrogen from water, using sunlight as energy. This process potentially can yield a virtually limitless source of pollution-free energy if technical and biochemical problems indigenous to the known hydrogen-producing organisms can be solved. Recombinant DNA techniques offer a possible means of solution to these problems.

It is ironic that some of the most vocal opposition to recombinant DNA research has come from those most concerned about the environment. The ability to manipulate microbial genes offers the promise of more effective utilization of renewable resources for mankind's food and energy needs; the status quo offers the prospect of progressive and continuing devastation of the environment. Yet, some environmentalists have been misled into taking what I believe to be an antienvironmental position on the issue of recombinant DNA.

The NIH Guidelines

Even if hazards are speculative and the potential benefits are significant and convincing, wouldn't it still be better to carry out recombinant DNA experiments under conditions that provide an added measure of safety—just in case some of the conjectural hazards prove to be real?

This is exactly what is required under the NIH (National Institutes of Health) guidelines (5) for recombinant DNA research:

1) These guidelines prohibit experiments in which there is some scientific basis for anticipating that a hazard will occur. In addition, they prohibit experiments in which a hazard, although it might be entirely speculative, was judged by NIH to be potentially serious enough to warrant prohibition of the experiment. The types of experiment that were the basis of the initial "moratorium" are included in this category; contrary to the statements of some who have written about recombinant DNA research, there has in fact been no lifting of the original restrictions on such experiments.

2) The NIH guidelines require that a large class of other experiments be carried out in P4 (high level) containment facilities of the type designed for work with the most hazardous naturally occurring microorganisms known to man (such as Lassa fever virus, Marburg virus, and Zaire hemorrhagic fever virus). It is difficult to imagine more hazardous self-propagating biological agents than such viruses, some of which lead to nearly 100 percent mortality in infected individuals. The P4 containment requires a specially built laboratory with airlocks and filters, biological safety cabinets, clothing changes for personnel, autoclaves within the facility, and the like. This level of containment is required for recombinant DNA experiments for which there is at present no evidence of hazard, but for which it is perceived that the hazard might be potentially serious if conjectural fears prove to be real. There are at present only four or five installations in the United States where P4 experiments could be carried out.

3) Experiments associated with a still lesser degree of hypothetical risk can be conducted in P3 containment facilities. These are also specially constructed laboratories requiring double door entrances, negative air pressure, and special air filtration devices. Facilities where P3 experiments can be performed are limited in number, but they exist at some universities.

4) Experiments in which the hazard is considered unlikely to be serious even if it occurs still require laboratory procedures (P2 containment) that have for years been considered sufficient for research with such pathogenic bacteria as *Salmonella typhosa*, *Clostridium botulinum*, and *Cholera vibrio*. The NIH guidelines require that P2 facilities be used for work with bacteria carrying interspecies recombinant DNA molecules that have shown no evidence of being hazardous—and even for some recombinant DNA experiments in which there is substantial evidence of lack of hazard.

5) The P1 (lowest) level of containment can be used only for recombinant DNA molecules that potentially can be made by ordinary biological gene exchange in bacteria. Conformity to even this lowest level of containment in the laboratory requires decontamination of work surfaces daily and after spills of biological materials, the use of mechanical pipetting devices or cotton plugged pipettes by workers, a pest control program, and decontamination of liquid and solid waste leaving the laboratory.

In other areas of actual or potential biological hazard, physical containment is all that microbiologists have had to rely upon; if the Lassa fever virus were to be released inadvertently from a P4 facility, there would be no further barrier to prevent the propagation of this virus which is known to be deadly and for which no specific therapy exists. However, the NIH guidelines for recombinant DNA research have provided for an additional level of safety for workers and the public: This is a system of biological containment that is designed to reduce by many orders of magnitude the chance of propagation outside the laboratory of microorganisms used as hosts for recombinant DNA molecules.

An inevitable consequence of these containment procedures is that they have made it difficult for the public to appreciate that most of the hazards under discussion are conjectural. Because in the past, governmental agencies have often been slow to respond to clear and definite dangers in other areas of technology, it has been inconceivable to scientists working in other fields and to the public at large that an extensive and costly federal machinery would have been established to provide protection in this area of research unless severe hazards were known to exist. The fact that

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recombinant DNA research has prompted international meetings, extensive coverage in the news media, and governmental intervention at the federal level has been perceived by the public as prima facie evidence that this research must be more dangerous than all the rest. The scientific community's response has been to establish increasingly elaborate procedures to police itself—but these very acts of scientific caution and responsibility have only served to perpetuate and strengthen the general belief that the hazards under discussion must be clear-cut and imminent in order for such steps to be necessary.

It is worth pointing out that despite predictions of imminent disaster from recombinant DNA experiments, the fact remains that during the past 3½ years, many billions of bacteria containing a wide variety of recombinant DNA molecules have been grown and propagated in the United States and abroad, incorporating DNA from viruses, protozoa, insects, sea urchins, frogs, yeast, mammals, and unrelated bacterial species into *E. coli*, without hazardous consequences so far as I am aware. And the majority of these experiments were carried out prior to the strict containment procedures specified in the current federal guidelines.

Despite the experience thus far, it will always be valid to argue that recombinant DNA molecules that seem safe today may prove hazardous tomorrow. One can no more prove the safety of a particular genetic combination under all imaginable circumstances than one can prove that currently administered vaccines do not contain an undetected self-propagating agent capable of producing cancer in the future, or that a hybrid plant created today will not lead to disastrous consequences some years hence. No matter what evidence is collected to document the safety of a new therapeutic agent, a vaccine, a process, or a particular kind of recombinant DNA molecule, one can always conjure up the possibility of future hazards that cannot be disproved. When one deals with conjecture, the number of possible hazards is unlimited; the experiments that can be done to establish the absence of hazard are finite in number.

Those who argue that we should not use recombinant DNA techniques until or unless we are absolutely certain that there is zero risk fail to recognize that no one will ever be able to guarantee total freedom from risk in any significant human activity. All that we can reasonably expect is a mechanism for dealing responsibly with hazards that are known to exist or which appear likely on the basis of information that is known. Beyond this, we can and should exercise caution in any activity that carries us into previously uncharted territory, whether it is recombinant DNA research, creation of a new drug or vaccine, or bringing a spaceship back to Earth from the moon.

Today, as in the past, there are those who would like to think that there is freedom from risk in the status quo. However, humanity continues to be buffeted by ancient and new diseases, and by malnutrition and pollution; recombinant DNA techniques offer a reasonable expectation for a partial solution to some of these problems. Thus, we must ask whether we can afford to allow preoccupation with and conjecture about hazards that are not known to exist, to limit our ability to deal with hazards that do exist. Is there in fact greater risk in proceeding judiciously, or in not proceeding at all? We must ask whether there is any rational basis for predicting the dire consequences of recombinant DNA research portrayed in the scenarios proposed by some. We must then examine the "benefit" side of the picture and weigh the already realized benefits and the reasonable expectation of additional benefits, against the vague fear of the unknown that has in my opinion been the focal point of this controversy.

References and Notes

1. P. Berg, D. Baltimore, H. W. Boyer, S. N. Cohen, R. W. Davis, D. S. Hogness, D. Nathans, R. Roblin, J. D. Watson, S. Weissman, N. D. Zinder, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 2593 (1974).
2. S. N. Cohen, A. C. Y. Chang, H. W. Boyer, R. B. Helling, *ibid.* **70**, 3240 (1973); S. N. Cohen, *Sci. Am.* **233** (No. 7), 24 (1975).
3. If we accept the view that any natural barriers to the propagation of genetic material derived from unrelated species do not owe their existence to the intent of nature, we can reason that evolution has created and maintained such barriers because opportunities for genetic mixing occur in nature. Furthermore, we must conclude that limitations to gene exchange have evolved because the mixing of genes from diverse organisms is biologically undesirable—not in a moral or theological sense as some observers would have us believe—but to those organisms involved.
4. E. Chargaff, *Science* **192**, 938 (1976).
5. *Fed. Reg.* **41**(176) (9 September 1976), pp. 38426–38483.

Mr. THORNTON. As we proceed this morning, if any members have any questions for clarification, particularly relative to the testimony just given, I will be pleased to recognize them for questions as we go along.

I do have one such question with regard to page 2 of your testimony, where, in the last full paragraph before the bottom of the page you state that: "We cannot, and we will not, make plans at the specific level, until the legislative and regulatory environment is clarified."

Then within about eight lines you state: "We are already making commitments in the hope that there will be many beneficial outcomes."

Can you please clarify that?

Dr. CAPE. I'll be glad to, Mr. Chairman. I've been asked that question several times.

When people ask us, "What are your plans?", I gather they're usually asking us, "What are you going to do?", and in that sense I can't say yet what we are going to do. I know that there are certain things which we will have to do, regardless of specifically which programs we undertake. We must hire staff. To get the best possible people requires long leadtimes. To get the necessary equipment requires long leadtimes. To build the proper containment facilities requires long leadtimes.

It's in that connection that I said we may be gambling, and we may lose. If it turns out that this work will never take place in the industrial community, then that money will have been wasted in large part.

Mr. THORNTON. I appreciate that clarification. I thought it was appropriate to have it immediately follow your testimony.

I will want to come back later on to your views on patent matters and on other aspects of your testimony.

Mr. Brown.

Mr. BROWN. Mr. Chairman, one of the difficult questions of policy that is going to arise in connection with private industry work in this area is the mode, if any, for regulating the activity. As I think you and others have pointed out, the NIH guidelines basically don't apply to industry, or they have no muscle in terms of their application to industry because they're basically guidelines that could be implemented by the withholding or not withholding of Federal grants.

I understand that in Britain there is a much more unified approach to this matter of regulation, that it's handled by the National Occupational Health and Safety Commission, which would make it applicable in any situation.

Do you have any suggestions as to how we could simplify this process of policy, regulation, in this area if it's determined necessary to go into it? We have OSHA; we have EPA; we have the Food and Drug Administration; we have all sorts of regulatory agencies. We seem to create new ones at the drop of a hat, which I regard as highly undesirable. What suggestions would you offer in that regard?

Dr. CAPE. Mr. Brown, the report to which I referred by Dr. Fredrickson, which was sent to Mr. Califano last week, addressed the point that the suggestion has been made by many people who think that perhaps we can move more quickly; that existing laws, OSHA, EPA, that sort of thing, do, in fact, cover many of the things about which people have expressed legitimate concern.

It turns out that Dr. Fredrickson's committee appointed a subcommittee which examined that question in some detail, and the document which I will submit goes into their conclusion, which is that unfortunately there simply is no way in which those who are concerned, and legitimately so, would be able to be satisfied that the situation was being properly handled that way and that new legislation and a new authority to administer this whole business is probably required.

Mr. BROWN. We've done that before. When the public became greatly concerned about nuclear safety, we set up what is now the Nuclear Regulatory Commission.

Do you want to see a biological regulatory commission set up?

Dr. CAPE. Mr. Brown, I certainly—and I think everybody shares with me—feel apprehensive about more bureaucracy. All I'm saying is that the legal minds addressed the specific teeth in the existing legislation and apparently found that there are some teeth missing.

Mr. BROWN. Thank you.

Mr. THORNTON. Thank you, Mr. Brown.

Dr. Cavalieri, do you have a comment that you think is appropriate to make at this time?

Dr. CAVALIERI. I would like to make a comment about the level of the discussion, if I might.

I think that rather than assume that we need regulation, which body should regulate, or best how to do it, that we first settle the question, the more important one: Do we even want to go ahead with the research? Then it would be appropriate to ask how to regulate it.

Mr. THORNTON. Dr. Baltimore.

Dr. BALTIMORE. Mr. Brown, I think the question you raise is very important. I have read the interagency report, and it clearly documents why no present legislation provides the correct umbrella to cover all areas that are involved in recombinant DNA research.

So the request is going to be made of Congress, has already been made of Congress, to pass legislation which is revolutionary because it covers a form of activity, scientific research, which has not previously been regulated, and you pointed that out very clearly.

So the reason that I would support this legislation, and I think many people would support it, although being very afraid of it, is not because the other agencies don't cover it, but rather, because what we are seeing now is the development of a patchwork of regulation across the country, whereby the State of California is considering its legislation; the city of Cambridge has passed its legislation; the city of Princeton, N.J. has its regulations; and that's an intolerable situation under which to carry out research activities.

If there is, as I will point out later, any danger in this area of research it will not obey political boundaries. It's an international problem.

So I think it's appropriate if there be any legislation that it be from the Congress, and if it's correct that there is no legislation there which can cover it, I think it's incumbent on the Congress to design such legislation. But recognizing, when moving into this area, as you point out, that it is a whole new ballgame, and one that should only be gone into with extreme care because one is bordering on the whole question of the freedom of thought, and when you reach that borderline legislation can be, as I'm sure you are well aware, very dangerous.

Mr. THORNTON. Thank you, Dr. Baltimore.

As I was about to mention, we've now looked at some of the commercial applications of the research, and want to turn to an assessment of various possible risks that have been attributed to this research technique.

I had the privilege of hearing the next witness, Dr. Daniel Nathans, at a National Academy of Sciences forum on March 7th, describe some of the benefits of this research.

Dr. Nathans, we are very pleased to have you with us today to provide us with an analysis of the risks involved in this research.

Dr. Nathans is from the Johns Hopkins University School of Medicine. We do have your prepared statement before us, and I would like to ask, if possible, that you summarize that statement at this time.

[A biographical sketch and prepared statement of Dr. Nathans follows:]

Daniel Nathans

Dr. Daniel Nathans is a microbiologist with past training in internal medicine and molecular biology. For the past six years he has been Professor and Director of the Department of Microbiology at The Johns Hopkins University School of Medicine in Baltimore, Maryland. In addition to teaching medical microbiology, molecular biology and genetics, he does research on tumor viruses. Recently one of his students and he have been using recombinant DNA's in their research.

Dr. Nathans' research has been supported by the National Institutes of Health, the American Cancer Society, and the Whitehall Foundation. He has served on advisory committees of the National Institutes of Health and the American Cancer Society and was a member of the National Academy of Sciences Committee on Recombinant DNA that called for a voluntary moratorium on certain recombinant experiments and for the development of research guidelines. He is now a member of the Advisory Committee for the Virus Cancer Program of the National Cancer Institute.

Testimony before the House Subcommittee on Science, Research and Technology. March 30, 1977.

Daniel Nathans, Professor and Director, Department of Microbiology, Johns Hopkins University School of Medicine.

I want to thank the members of the Committee for giving me this opportunity to express my views on recombinant DNA research. Before getting to the substance of what I have to say let me identify myself. I am a microbiologist with past training in internal medicine and molecular biology. For the last six years I have been Professor and Director of the Department of Microbiology at the Johns Hopkins University School of Medicine in Baltimore. In addition to teaching medical microbiology, molecular biology, and genetics, I do research on tumor viruses. Recently, one of my students and I have been using recombinant DNAs in our research. My research has been supported by the National Institutes of Health, the American Cancer Society, and the Whitehall Foundation, and my salary is paid by the Johns Hopkins University. I have served on Advisory Committees of the National Institutes of Health, and the American Cancer Society, and I was a member of the National Academy of Sciences Committee on Recombinant DNA that called for a voluntary moratorium on certain recombinant DNA experiments and for the development of research guidelines. I am now a member of the Advisory Committee for the Virus Cancer Program of the National Cancer Institute. The main points I want to make in this testimony are:

1) Recombinant DNA methodology represents a truly major development holding high promise for understanding normal and abnormal life processes of complex organisms including man, and for the solution of certain important medical problems.

2) With some exceptions the potential risk to public health from recombinant DNA research is likely to be very low.

3) The NIH guidelines on recombinant DNA research are a conservative response to those potential risks.

Recombinant DNA technology is an outgrowth of three decades of research in the genetics of microbes. It allows biologists to apply to complex organisms powerful analytical methods of microbial genetics and biochemistry, and also allows them to extend these techniques considerably by adding an ability to synthesize new gene combinations. I won't dwell on the expected benefits of recombinant DNA research, since I have been asked to concentrate primarily on an analysis of risks, but I would like to summarize my views on the biomedical benefits very briefly.

Probably the most far-reaching and the surest biomedical benefit will be the profound insights into the genetic basis of human development and disease. The practical implications of this knowledge we can only barely see. Shorter term, probable benefits are the produc- of human and microbial proteins useful in medical research or in the treatment and prevention of disease. Still other potential benefits, frankly speculative and more distant, include possible new ways to treat or prevent genetic disorders.

Now to the potential hazards of DNA recombinant research. From the very beginning scientists have been concerned about protecting the public from possible harm due to recombinant microbes. How does one assess the hazards of such microbes? We need to begin with

general comments on microbes and microbial pathogenicity. We live in a microbial world. Microbes are all about us, packed within our digestive tracts, on our skin, in the air we breathe, in the food we eat. The earth is populated with a wonderful variety of microbes. Each kind is a specialist and lives where it does because it has adapted to its environment over long periods of time, and thereby outgrows or accommodates to competing microbes. Each has its own turf. That tiny fraction of microbes that cause disease is also made up of extreme specialists. In the course of evolution they have acquired a complex genetic makeup that allows them to overcome the body's defenses in one way or another and in some cases also to spread in populations. When grown artificially in the laboratory, pathogenic microbes commonly lose their disease producing power by mutation. What was once a virulent organism become harmless.

What is the relevance of this to the question of hazards of recombinant research? Well, one of the basic concerns is that when an animal or a plant gene is put into the harmless laboratory strain of E. coli K12 (a bacterium derived several decades ago from human feces and used widely for recombinant studies) that this strain might become pathogenic, and indeed that it might cause serious epidemic disease. In my judgment, and in the judgment of experts in the field of intestinal infections this is a highly unlikely possibility. First of all, E. coli K12 after decades of growth in artificial media has lost its ability to colonize the bowel except under very unusual circumstances as shown by direct feeding tests. Unless conditions are rigged to give it a growth advantage, it doesn't

have a chance against the bacteria already there. Second, the ability of a microbe to cause disease, and particularly epidemic disease, is dependent on having an appropriate set of specialized genes, each of which is needed for pathogenicity. Moreover, the spread of intestinal bacterial pathogens is clearly dependent on poor sanitary measures or improper sewage disposal. It would therefore be very difficult, perhaps not possible, even purposely to turn K12 into some sort of plague bacillus.

There are more subtle hazards that also need to be examined. One of these is based on the demonstrated ability of E. coli K12 to transfer genes to other E. coli strains already in the bowel. Could harmful recombinant genes be spread in this way? Conceivably, yes, and that is why multiply defective K12 strains with very low survival and exceedingly low potential for gene transfer have been developed and why we need to minimize the persistence of recombinant genes in other ways as well. But even were recombinant genes to be transferred in spite of these precautions, unless these genes helped their host bacteria to grow better than their natural competitors, available evidence indicates that such genes are likely to be quickly lost.

Another subtle possible hazard first raised in the "moratorium letter" has to do with the spread of cancer-producing genes either in recombinant bacteria or recombinant viruses. We know there are such genes in many viruses, that almost all of us have been infected with these viruses, and that we generally harbor them in a hidden form throughout our lives. Would similar genes present in weakened E. coli K12 or in recombinant defective viruses be likely to increase

the risk of cancer? We cannot give an experimentally verified answer to this question, but a reasonable judgment is that such defective recombinants would not be as infectious and therefore not as hazardous as the natural pathogenic viruses to which we have already been exposed and to which we continue to be exposed. As I indicate later, the uncertainty in this area is taken into account in the NIH guidelines.

Another type of potential risk discussed with poetic force by Robert Sinsheimer is the long term risk of altering microbial evolution in ways inimicable to ourselves and to our environment. As Sinsheimer put it, "Nature has developed strong barriers against genetic interchange between species. What do we know of the consequences of breaching these barriers? In particular and specifically, what may in time ensue if we introduced genetic intercourse between ourselves ... and the ubiquitous microorganisms with which we live so intimately?" Although I know of no sure answers to this concern, I would point out that the intimacy between microbes and other life forms might already include genetic interchange. Microbes decompose us when we die. They are exposed to the plant and animal foods we eat, and to large numbers of cells shed in our intestinal tracts or on our body surfaces. In certain common diseases bacteria or other microbes persist for years inside human cells. And some cellular organelles are widely thought to have evolved from intracellular bacteria. It therefore seems likely, but by no means certain, that some bacteria regularly take up DNA from animal and plant sources. In the case of viruses, natural recombination with cellular DNA is an established fact. Perhaps experiments can be devised to determine

whether this is so with bacteria also. Another point relevant to Sinsheimer's question is one I discussed earlier, namely, the very low probability that unselected foreign genes will survive in nature, particularly with the kinds of microbes required by recombinant experiments under the NIH guidelines. Therefore, though we cannot know for certain "what may in time ensue," I believe there are substantial arguments aginst expecting the worst.

To sum up my views on biohazards: Up to the present time, and admittedly this is a short time, there is no reason to believe that research with recombinant DNA has led to the emergence of harmful microbes. Based on what is known of natural selection in the microbial world, the mechanisms of pathogenicity and spread of microbes, and the properties of defective microbes used in recombinant DNA research, the probability is very low that recombinants constructed under the NIH guidelines will be capable of survival in the natural world or spread in populations.

Having come to these conclusions, I do not want to leave you with the impression that available evidence excludes the possibility that harmful microbes will emerge from recombinant DNA research. That is not the case. Although I believe this eventuality is unlikely, for the reasons I indicated, clearly one can never disprove possibilities of this sort. Experiments to test survival and pathogenicity of particular recombinants, now being planned, may change our judgments, but they are not likely to resolve many uncertainties. It was just these considerations that led to the original call for a pause in specific recombinant experiments and to the NIH guidelines. Because

of the uncertainty, researchers are required under the guidelines to use levels of physical and biological containment far in excess of what has been common and successful practice for many decades in the safe handling of known pathogenic microorganisms, such as those causing typhoid fever, or diphtheria, or pneumonia. In this sense the guidelines are conservative, providing a margin of safety beyond what is probably needed. Given the uncertainties and the preeminent need to protect the public and those involved in recombinant DNA research, such conservatism is clearly warranted.

Thank you.

STATEMENT OF DANIEL NATHANS, PROFESSOR, DEPARTMENT OF MICROBIOLOGY, THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MD.

Dr. NATHANS. Let me thank the members of the committee for asking me to express my views.

I would like to identify myself. I'm a microbiologist with past training in internal medicine and molecular biology. I'm now professor and director of the Department of Microbiology at the Johns Hopkins University School of Medicine. In addition to teaching medical microbiology, molecular biology, and genetics, I do research on tumor viruses.

Recently one of my students and I have been using recombinant DNA's in our research. Our research has been supported by private foundations and public agencies, and my salary is paid by The Johns Hopkins University School of Medicine.

The main points I want to make in this testimony are:

First, that recombinant DNA methodology represents a truly major development. I won't dwell on this point. I have covered it in other testimony, and since I have been asked to concentrate on an analysis of risks, I won't say more about that, although I would be happy to elaborate on that later on if there are any questions.

My second point is that with some exceptions, the potential risk to public health from recombinant DNA research is, in my opinion, likely to be very low.

Third, that the NIH guidelines on recombinant DNA research are a conservative response to those potential risks.

In regard to potential hazards of recombinant DNA research, from the very beginning scientists have been concerned about protecting the public from possible harm due to recombinant microbes. How does one assess the hazards of such organisms? We need to begin with a general picture of microbes and microbial pathogenicity. We live in a microbial world. Microbes are all about us, packed within our digestive tracts, on our skin, in the air we breathe, in the food we eat. The Earth is populated with a wonderful variety of microbes. Each kind is a specialist and lives where it does because it has adapted to environment over long periods of time, and thereby outgrows or accommodates to competing microbes. Each has its own turf. That tiny fraction of microbes that cause disease is also made up of extreme specialists. In the course of evolution they have acquired a complex genetic makeup that allows them to overcome the body's defenses in one way or another, and in some cases also to spread in populations, When grown artificially in the laboratory, pathogenic microbes commonly use their disease-producing power by mutation. What was once a virulent organism becomes harmless.

What is the relevance of this to the question of hazards of recombinant DNA research? One of the basic concerns is that when an animal or a plant gene is put into the harmless laboratory strain of *E. Coli* K12—a bacterium derived in 1922 from human feces and widely used for recombinant studies—the concern is that this strain might become pathogenic, and indeed, that it might even cause serious epidemic disease. In my judgment, and in the judgment of experts in the field of intestinal infection, this is a highly unlikely possibility. First

of all, *E. coli* K12 after decades of growth in artificial media has lost its ability to colonize the human bowel except possibly under very unusual circumstances, as shown by direct feeding tests. Unless conditions are rigged to give it a growth advantage, ingested *E. coli* doesn't have a chance against the bacteria already there.

Second, the ability of a microbe to cause disease, and particularly epidemic disease, is dependent on its having an appropriate set of specialized genes, each of which is needed for pathogenicity. Moreover, the spread of intestinal bacterial pathogens is clearly dependent on poor sanitary measures or improper sewage disposal. It would therefore be very difficult, perhaps not possible, even purposely to turn K12 into some sort of plague bacillus.

There are more subtle hazards that also need to be examined. One of these is based on the demonstrated ability of *E. coli* K12 to transfer genes to other *E. coli* strains already in the bowel. Could harmful recombinant genes be spread in this way? Conceivably, yes, and that is why multiple defective K12 strains with very low survival and exceedingly low potential for gene transfer have been developed and why we need to minimize the persistence of recombinant genes in other ways as well. But even were recombinant genes to be transferred in spite of these precautions, unless these genes helped their host bacteria to grow better than their natural competitors, available evidence indicates that such genes are likely to be quickly lost.

Another subtle possible hazard first raised in the "moratorium letter" has to do with the spread of cancer-producing genes either in recombinant bacteria or recombinant viruses. We know there are such genes in many viruses, that almost all of us have been infected with these viruses, and that we generally harbor them in a hidden form throughout our lives. Would similar genes present in weakened *E. coli* K12 or in recombinant defective viruses be likely to increase the risk of cancer? We cannot give an experimentally verified answer to this question, but a reasonable judgment is that such defective recombinants would not be as infectious and therefore not as hazardous as the natural pathogenic viruses to which we have already been exposed and to which we continue to be exposed. As I indicate later, the uncertainty in this area is taken into account in the NIH guidelines.

Another type of potential risk discussed with poetic force by Robert Sinsheimer is the long-term risk of altering microbial evolution in ways inimicable to ourselves and to our environment. As Sinsheimer put it:

> **Nature has developed strong barriers against genetic interchange between species. What do we know of the consequences of breaching these barriers? In particular and specifically, what may in time ensue if we introduced genetic intercourse between ourselves * * * and the ubiquitous micro-organisms with which we live so intimately?**

Although I know of no sure answers to this kind of concern, I would point out that the intimacy between microbes and other life forms might already include genetic interchange. Microbes decompose us when we die. They are exposed to the plant and animal foods we eat, and to large numbers of cells shed in our intestinal tracts or on our body surfaces. In certain common diseases bacteria or other microbes persist for years inside human cells. And some cellular organelles are widely

thought to have evolved from intracellular bacteria. It therefore seems likely, but by no means certain, that some bacteria regularly take up DNA from animal and plant sources. In the case of viruses, natural recombination with cellular DNA is an established fact. Perhaps experiments can be devised to determine whether this is so with bacteria also. Another point relevant to Sinsheimer's question is one I discussed earlier, namely, the very low probability that unselected foreign genes will survive in nature, particularly with the kinds of microbes required by recombinant experiments under the NIH guidelines. Therefore, though we cannot know for certain "what may in time ensue," as Sinsheimer put it, I believe there are substantial arguments against expecting the worst.

To sum up my views on biohazards: Up to the present time, and admittedly this is a short time, there is no reason to believe that research with recombinant DNA has led to the emergence of any harmful microbes. Based on what is known of natural selection in the microbial world, the mechanisms of pathogenicity and spread of microbes, and the properties of defective microbes used in recombinant DNA research, the probability is very low that recombinants constructed under the NIH guidelines will be capable of survival in the natural world or spread in populations.

Having come to these conclusions, I don't want to leave you with the impression that available evidence excludes the possibility that harmful microbes will emerge from recombinant DNA research. That is not the case. Although I believe this eventuality is unlikely, for the reasons I've indicated, clearly one can never disprove possibilities of this sort. Experiments to test survival and pathogenicity of particular recombinants, now being planned, may change our judgments, but they are not likely to resolve many uncertainties. It was just these considerations that led to the original call for a pause in specific recombinant experiments and to the NIH guidelines. Because of the uncertainty, researchers are required under the NIH guidelines to use levels of physical and biological containment far in excess of what has been common and successful practice for many decades in the safe handling of known pathogenic micro-organisms, such as those causing typhoid fever, or diphtheria, or pneumonia. In this sense the guidelines are conservative, providing a margin of safety beyond what is probably needed. Given the uncertainties and the preeminent need to protect the public and those involved in recombinant DNA research, such conservatism is clearly warranted.

Thank you.

Mr. THORNTON. Mr. Ottinger.

Mr. OTTINGER. I want to thank the chairman, first of all, very much for allowing me to participate in these hearings. I'm on the full committee, but not on this subcommittee, and Mr. Thornton very graciously invited me to participate because I have been involved in this issue, particularly in my service on the Health and Environment Subcommittee of the Commerce Committee. I do thank him.

Do you want to wait for questions until all of the witnesses have finished their statements?

Mr. THORNTON. Unless they are necessary to clarify the particular testimony, I would prefer that we wait and address them to the panel as a whole.

But I did want to recognize you, and we appreciate your being here.

Mr. OTTINGER. I will wait for members of the subcommittee then. I just wanted to thank you very much for this opportunity to participate.

Mr. THORNTON. Thank you.

While most of the risks and benefits which have been perceived so far seem to be associated with problems in the biomedical sciences, it's not the only concern.

Yesterday, Dr. Charles Lewis testified with regard to certain benefits that might be derived from agricultural research.

Our next speaker, Dr. Ethan Signer, who is professor of biology at MIT, has worked in the past on related research in nitrogen fixation. We had some very good testimony recently in the Agriculture Committee on that subject with regard to the agricultural research bill, which I sponsored.

Dr. Signer, we would like to ask your perceptions of some of the risks associated with DNA recombinant research, extending beyond the biomedical sphere of discussion.

Again, we do have your prepared statement, which, without objection, will be made a part of the record. I would like to ask you now to proceed to summarize that statement.

[A biographical sketch of Dr. Signer follows:]

Curriculum Vitae

Name: Ethan R. Signer

Birthdate: April 3, 1937

Place of Birth: Brooklyn, New York

Nationality: U.S. citizen

Social Security No: 074-30-8328

Education: Yale University, New Haven, Conn.; B.S. Biophysics, 1958

Mass. Inst. of Tech., Cambridge, Mass.; Ph.D. Biophysics, 1963.

Med. Res. Counc. Lab. Molec. Biol., Cambridge, England; Postdoctoral fellow, 1962-1964.

Honors: Yale University: B.S. Magna cum Laude, High honors in Biophysics

Career Development Awardee, U.S. Public Health Service, 1967-1972

Research and/or Professional Experience:

July, 1972 - present: Professor of Biology, Massachusetts Institute of Technology, Cambridge, Mass.

1968 - July, 1972 : Associate Professor of Microbiology, Massachusetts Institute of Technology, Cambridge, Mass.

1966 - July, 1968 : Assistant Professor of Microbiology, Massachusetts Institute of Technology, Cambridge, Mass.

1964 - 1966 : Postdoctoral fellow, laboratory of Dr. F. Jacob, Institut Pasteur, Paris, France.

1962 - 1964 : Postdoctoral fellow, laboratory of Dr. S. Brenner, Medical Research Council Laboratory of Molecular Biology, Cambridge, England.

Ph.D. thesis work : Massachusetts Institute of Technology; thesis advisor Dr. C. Levinthal; Study of the isoenzymes of *E. coli* alkaline phosphatase, and of the expression of the alkaline phosphatase gene of *E. coli* in the cytoplasm of *S. marcescens*.

Publications:

See attached list

PUBLICATIONS OF DR. E.R. SIGNER

1. 1961. Bach, M.L., Signer, E.R., Levinthal, C. and Sizer, I.W. Electrophoretic Patterns of Alkaline Phosphatase from Various E. coli Mutants. Fed. Proc. 20: 255.

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10. 1966. Beckwith, J.R. and Signer, E.R. Transposition of the Lac Region of E. coli. I. Inversion of the Lac Operon and Transduction of Lac by φ80. J. Mol. Biol. 19: 254-265.

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44. 1976. Ludwig, R.A. and E. Signer. Nitrogen Fixation in Free Living Rhizobia. The 76th Annual Meeting of the American Society for Microbiology, p. 164.

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[The prepared statement of Dr. Signer is as follows:]

STATEMENT OF ETHAN SIGNER, PROFESSOR OF BIOLOGY, MASSACHUSETTS INSTITUTE OF TECHOLOGY

RECOMBINANT DNA IS NO MIRACLE CURE

My name is Ethan Signer. I am Professor of Biology at the Massachusetts Institute of Technology.

I want to thank the subcommittee for giving me the opportunity to speak. This issue has brought us to a critical point with regard not only to genetic research but to the role of science in our society. We scientists don't necessarily know best. These are larger matters than we can handle alone. We need the public, working through Congress in the democratic process, if we're to resolve them in a way that's productive for all of us.

My own field is the molecular genetics of bacteria and their viruses. Until a few years ago, I worked with the colon bacterium *E. coli*, in the fundamental areas of gene regulation and recombination. Then I decided to change my focus to an area that, while still basic research, had more direct application. I started to work on nitrogen-fixation, the process by which microorganims take nitrogen out of the air, and convert it to a form that can be used by plants and ultimately, through what we eat, by us.

Our group was eager to transfer the genes for nitrogen fixation from the bacteria directly into plant cells. With those genes, the plants might fix their own nitrogen, and so not have to depend either on bacteria or on chemical nitrogen fertilizer. This is the same experiment some scientists want to do now with recombinant DNA technology, but at the time we had only the tedious, uncertain biological methods.

Recombinant DNA seemed ideal for us when it came along. Yet after a long series of discussions we decided to stay away from it. It seemed too hazardous, in ways I'll discuss in a moment. So we continued with the old methods, but then we stopped even that. Our methods were safe, but the results smacked too much of the image of science that had become associated with recombinant DNA technology. We felt a bit too uncomfortable working on what was being billed as a miracle solution for the world food problem. This was at a time when the previous miracle solution, the Green Revolution, was turning out to be a failure in Asia, not feeding people, but rather making the rich richer and the poor even poorer. So we went back to pure research, though with these same bacteria. And as it happens, what we're finding now might have deep implications for nitrogen and fertilization.

As for the world food problem, I don't think it's going to miss us. There are a billion malnourished people on the planet, a quarter of us all. Yet, according to a World Bank study, the number of calories needed to feed them all amounts to a mere 4 percent of the world annual grain production. Learning to do without fertilizer won't change that. That malnourishment has to do with the distribution of income and political power, with relations among sectors of society within nations and among nations themselves. Those are political problems, so of course technological solutions, while perhaps changing their terms somewhat, can't possibly solve them.

In other words, to consider this as a case in point regarding the benefits of recombinant DNA research: they're not the ones we really need; we can get them other ways; and having them won't really solve the problems they're meant for.

It's the same for nearly all the benefits the advocates of this research claim. It's supposed to give us more insulin. But it would be much simpler to improve the isolation methods for the hog insulin that works very well right now; and recombinant DNA won't give us cheaper insulin, since as we know the drug industry doesn't pass on savings to the consumer. Another case—"a notable and promising example", Dr. Nathans has called it—is the use of this technology to develop a vaccine against cholera. The real solution to that problem is proper sanitation, which would completely control cholera. That would be cheaper and easier, and much more beneficial to the people who are subject to this disease. In that way it's like the cancer problem. The consensus now is that most if not all cancers have environmental causes and can in principle be prevented. Yet we keep hearing that it's recombinant DNA technology that will bring us a solution.

What we really need in medicine is more doctors and hospitals, a more humane and dignified approach to treatment, a more equal distribution of what we have

and could have right now. Everybody knows how bad medical care has become, and recombinant DNA certainly won't change that.

And as far as basic research benefits go, there are many, many others to be had. Recombinant DNA isn't a Truth, it isn't a Fundamental Law of Nature it isn't Pure Knowledge. It's a tool for getting at those things, but there are other tools, and we will come up with still others. There are other ways to study what we're using recombinant DNA for, and for that matter, many other things, a whole biosphere, left to study if we're interested in basic research. Eliminating recombinant DNA research would be just like eliminating other tools that are too dangerous, such as vivisection, for example, or experimenting on people without their consent.

It is dangerous, not least because of leakage, breakdown or human error, which are always possible, but for other, subtler reasons as well. Whatever the guidelines, the required levels for a given experiment are bound to drift slowly downward as time goes on, until the accident finally happens. Competition in science is already ferocious. We scientists are no different from anyone else, we're just as eager for success. The Cetus Corporation, formed specificially to exploit molecular biology, acknowledges that "It is . . . still difficult to find any really important medical or industrial capability for which it matters at all that we know the genetic code . . ." Yet they go on to propose "to create an entire new industry to [focus] on those specific problems that appear most amenable to solution . . . and promise the best cost-benefit ratio." That's not a very reassuring attitude toward a hazardous course of action.

Recombinant DNA is an extraordinarily simple technique to work with. Anyone can use it. There is no way to deduce the level of containment used in making a particular hybrid, especially in a high security industrial laboratory, where sooner or later a large spill will contaminate some unfortunate technician who didn't even know what was in the vat. Nobody seriously believes it will be possible to police the drug companies. And the longer we go without an accident, the more used to this technology we'll become. We'll move from high-level to low-level containment to large scale production, until one day we find that one of the recombinant DNA's we've let loose has some properties we hadn't predicted. Perhaps it makes a crippled bacterium infectious again, or triggers an unexpected digestive difficulty or antibody response in people, or makes a further hybrid in nature with a virus we didn't even know existed, and starts an epidemic. Five years ago we couldn't even predict we'd be using recombinant DNA technology. We know next to nothing about ecological balances, even among organisms we're familiar with, let alone recombinants no one has made before. And there's no way to measure the risk of any of this.

What's more, there is one danger that's quite certain, and that is human genetic engineering. This technique brings us one giant step closer to it, and the closer we get, the harder it will be to stop. The kind of attitude that's going to make it a reality is the one, for example, of Edward Teller, father of the hydrogen bomb, who said "I believed in the possibility of developing a thermonuclear bomb. My scientific duty demanded exploration of that possibility". If genetic engineering seems far off, let's remember how unlikely walking on the moon used to seem when we were children.

It's no source of pride to see how science is sometimes used to defend and justify, and even perpetuate, inequities in our society. From the eugenics movement many years ago through IQ testing more recently to sociobiology, right now, some people desperately try to use science to prove that those who have ought to have, while those who don't have don't deserve. When we learn how to manipulate people's genes, then some of us will do the manipulating, while others have their genes manipulated. Some of us will decide for the rest of us what constitutes a normal or desirable type of person, and that won't be pretty. Let's not forget that killing off people who didn't have blond hair, blue eyes and whatever Aryan heritage means was, however crude, an attempt at genetic engineering, one that came altogether too close to succeeding.

These are some of the reasons why people I've talked to are frightened of this research, and I don't think they're crazy to be so. That's not irrational fear of the unknown, it's rational sensible fear of the unknown.

Dr. Baltimore has said, about the recent debate in Cambridge, that when non-scientists became involved, it wasn't because they don't trust us scientists to regulate ourselves. The people I've talked to lead me to the opposite conclusion. For some time now we've been hearing about the anti-science backlash, a mistrust of science in general among the public. Part of that is surely due to

the way spectaculars like recombinant DNA are promoted. That can't help but raise false expectations and end by giving science a bad name. People are told over and over about swine flu vaccines, war on cancer, heart transplants, recombinant DNA and so forth. But these are hard to reconcile with what you can actually get in the way of practical medical care. So perhaps the public is beginning to say, "Enough propaganda, enough mysterious doubletalk, enough promises, enough miracle cures, enough spectaculars". Perhaps people aren't so eager to trust us to tinker with their genes in the name of their welfare.

As I said earlier, we're at a critical point regarding the role of science in our society. Even in this country the social and economic situation is clearly more tenuous than it was back in the days when our largest city wasn't nearly bankrupt and when a nationwide fuel shortage in peacetime was unimaginable. The phenomenal expansion of our overall scientific endeavor that was touched off by the Soviet Sputnik only 20 years ago has developed enormous momentum. It may well become an independent, self-sustaining, ungovernable enterprise if it is not soon integrated with the rest of society and made, if not more responsive to, then at least more consistent with its needs.

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"This is a matter far too important to be left solely in the hands of the scientific and medical communities. The belief that . . . [it is] inevitable because science always moves forward respresents a form of laissez-faire nonsense dismally reminiscent of the credo that American business if left to itself will solve everybody's problems. Just as the success of a corporate body in making money need not set the human condition ahead, neither does every scientific advance automatically make our lives more 'meaningful'. . . . A blanket declaration of worldwide illegality might be one result of a serious effort to ask the world in which direction it wishes to move . . . [if] we do not think about the matter now, the possibility of having a free choice will one day suddenly be gone."

STATEMENT OF ETHAN SIGNER, PROFESSOR OF BIOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASS.

Dr. SIGNER. Thank you, Mr. Chairman.

My name is Ethan Signer. I am professor of biology at the Massachusetts Institute of Technology.

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I want to close by quoting an eloquent statement by Dr. James Watson, one of our country's foremost scientists. He is an advocate of recombinant DNA, which he works on. Six years ago he had this to say before the panel on science and technology of this committee, then the House Committee on Science and Astronautics, about another tool for genetic engineering, called cloning, which he wasn't working on:

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Thank you very much, Mr. Chairman.

Mr. THORNTON. Thank you very much, Dr. Signer, for a very provocative and interesting statement. I'm sure that there will be a number of questions as we get on further into hearing from the rest of our witnesses.

I would like to make one quick observation, and that is that I'm always concerned when the institutions of Nazi Germany are cited in support of or in opposition to a particular course of behavior because, just as that regime may have engaged in barbarous acts of human behavior, which could be likened to genetic engineering, it seems to me that I recall they also burned books and tried to limit the expansion of knowledge. So the citation is to be applied, I think, to both sides of the equation.

Dr. SIGNER. Definitely.

Mr. THORNTON. Thank you very much, Dr. Signer.

Our fourth witness has been quite outspoken in his concern about the continuation of DNA recombinant research. Dr. Cavalieri is a researcher at the Sloan-Kettering Institute for Cancer Research, and he sees a number of risks in this area which he believes require serious, thoughtful consideration.

Dr. Cavalieri, we appreciate your being with us. We do have your prepared statement, which will, without objection, be made a part of the record. We invite your observations at this time.

[A biographical sketch of Dr. Cavalieri follows:]

BIOGRAPHY

CAVALIERI Liebe Frank M August 26 1919
Name.....Sex.....Date of Birth.....
Last First Middle Month Day Year

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145 Boston Post Road, Rye, New York 10580 914 OW 8 1100 x 304/305
Office Address.....Tel. No. .....

Married Barbara H. 1
Marital Status.....Name of Spouse.....No. of Dependents: Children.....
Spouse.....
Other.....

Philadelphia Pennsylvania U.S.A. U.S.A.
Birthplace.....Citizenship.....
City State Country

Colleges or Universities Attended	Location	Degree Awarded	Year
University of Pennsylvania	Philadelphia, Pa.	B.S.	1943
		M.S.	1944
		Ph.D. (chem)	1945

Research and Academic Appointments	Institution	Dates
Post-doctoral Fellow in Chemistry	Ohio State University	1946
Research Chemist	Sloan-Kettering Institute for Cancer Research	1946
Research Fellow	"	1946-1947
Research Assistant	"	1948-1950
Research Associate	"	1950-1960
Member	"	1960-
Assistant Professor of Biochemistry	Sloan-Kettering Division Graduate School of Medical Sciences, Cornell University Medical College	1952-1954
Associate Professor of Biochemistry	"	1954-1960
Professor of Biochemistry	"	1961-
Chairman, Committee for Graduate Studies	"	1957-1961
Associate Director	"	1961-1968

Scientific and Medical Societies

Alpha Chi Sigma - 1943
American Association for the Advancement of Science - 1943
American Chemical Society - 1943
Sigma Xi - 1946
American Society of Biological Chemists - 1950
American Society for Cell Biology - 1972

Sabbatical Leaves

Institut de Recherches Scientifique sur le Cancer	1970-1971
Columbia University	1950-1951

STATEMENT OF DR. LIEBE CAVALIERI, RESEARCHER, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH, RYE, N.Y.

Dr. CAVALIERI. Thank you very much, Mr. Thornton. I thank you for inviting me to participate in these hearings.

I am a member of the Sloan-Kettering Institute for Cancer Research and a professor of biochemistry in the Graduate School of Medical Sciences of Cornell University. I have been involved in DNA moleclar biological research for 25 years, but I am not now nor do I ever intend to carry on laboratory investigative work in the field of recombinant DNA.

You have heard Drs. Cape and Nathans extoll the virtues of recombinant DNA technology. I would emphasize that the only certain scientific benefit is a better understanding of DNA function in animal and human cells. You also have heard of the potential technological benefits—those involving the production of insulin, hormones, and so forth. You have heard very little about the long-range applications of the technology and their possible bearing on human welfare, human freedom, and human dignity. Scientists and industrialists are not especially qualified to speak on these subjects. However, we all, as members of society, had better address ourselves to these questions very soon if we are to arrive at a same solution to what is one of the greatest societal dilemmas of the 20th century.

I will start by stating my position quite positively: I am opposed to recombinant DNA technology at present and until such time as adequate, enlightened and disinterested consideration and discussion has occurred among various groups, including nonscientific professionals and the lay public. These and other recent hearings represent first attempts at sober discussion to be followed by deep reflection. As members of what I hope is still a respected community—the scientific community—I hope that we can make a contribution to your understanding of the problem. However, I believe that the final evaluations and decisions must be made by society at large, and its representatives rather than by scientists.

I will try to be as specific as possible in my commentary since I am sure you are all aware of and perhaps satiated with generalizations.

First, concerning the probability of an accident. In the normal working day an investigator working with recombinant DNA proceeds step by step through literally hundreds of operations. To attach a probability value to a mishap in any one of these is to try to quantify human error. This is impossible. It can lead to no meaningful number. As you know, biological containment has been proposed by the NIH guidelines to minimize the dangers that could result from an accident. This means, at present, that a weakened strain of *E. coli* is used for recombinant DNA experiments. When these bacteria enter an inappropriate medium they are designed to commit suicide. They are expected to behave in this way if they enter the human intestinal tract, but the exact length of time required for the suicidal act there is not known, nor has it been established whether it may sometimes be possible for these cells to transfer recombinant DNA to one of the many other types of healthy *E. coli* found there. If there were a transfer of DNA to these healthier bacteria the recombinant genes could then easily become part of the biosphere. The probability of this series of events is not known,

but it must be taken seriously since even the most stringent physical containment facilities cannot exclude human beings with intestinal tracts, nor can they totally eliminate the possibility of accidents.

Another safeguard incorporated by the NIH guidelines is the specification that under certain conditions the more dangerous experiments involving recombination of DNA from unrelated species must utilize DNA fragments which have been identified and purified to the extent of 99 percent. Thus, few unknown or dangerous genes would be present. In reality, however, it is not only very difficult to achieve this degree of purity, but it is essentially impossible to prove it, in the case, say, of human DNA. The methods available are just not that refined. I emphasize, therefore, that the phrase "99 percent pure" is open to individual interpretation, and the guidelines thus create a feeling of safety which is not warranted.

In this connection, there is an even more disturbing and unpredictable factor which cannot even enter any of the hypothetical calculations for risk. This does not concern merely the physical purity of the DNA but, more importantly, its genetic purity. In the February issue of the journal Nature an illustrious group at Cambridge, England, headed by Prof. Fred Sanger, has reported a surprising new fact about DNA from a bacterial virus. Up to the present each section of a DNA molecule was believed to contain the genetic information for a single protein. But these workers have shown that a pure DNA fragment, coding for a specific protein, may contain overlapping information and can also specify a second protein. If such a "pure" DNA fragment were used for recombinant DNA experiments, bacteria might be produced which could manufacture not only the desired product but also another, unexpected one which might be dangerous.

The question of the purity of the DNA fragment in such an instance would be meaningless. The writers of the NIH guidelines did not bargain for this complication. I bring up this point to illustrate the fact that there are hidden traps everywhere—as any scientist will attest; it is axiomatic in science that such surprises are the rule rather than the exception. The discovery of overlapping genes by Professor Sanger and his colleagues represents not merely a new wrinkle in molecular biology but to my mind it emphasizes most vividly the certainty of uncertainty in an area where we can ill afford to take chances.

Dr. Halsted Holman, a professor of medicine at Stanford Medical School and a primary-care physician, has raised an interesting but disturbing problem. He notes that *E. coli* infections of the bloodstream cause a large number of deaths and that the incidence of infections is on the increase. He feels that three factors contribute to this situation:

One: Increase in the elderly population requiring health care;

Two: Increased prevalence of chronic diseases; and

Three: Increase in use of drugs which inhibit the immune response.

He notes, further, that:

Much research on recombinants is done in medical centers where there is considerable exchange between the people working in the laboratories and people seeing patients. Sometimes the same person does both. Thus, we have a different epidemiological problem from the one envisioned in the guidelines. It is the problem of enfeebled bacteria interacting with some persons whose resistance is compromised. It is a question of the epidemiology of infection of weakened human hosts with altered bacteria. Techniques for monitoring and controlling this situation are, at least to my knowledge, not well developed.

Nonetheless, P3 and perhaps even P4 recombinant research facilities are now being built in many medical centers. This represents to me the height of irresponsibility.

I will conclude my commentary on accidental dangers by observing that a very low probability coupled to a high-risk event leads inevitably to the area of value judgment. When this occurs we have a public issue which requires a political solution, not a scientific one. The low probability that a flame retardant would be confused with animal food was of no consolation to the large number of people in Michigan whose health and property were thereby damaged or destroyed. A nuclear disaster could affect millions of people and must be still more carefully guarded against, however low its probability.

In the case of recombinant DNA technology we have even greater cause for concern, for a genetic disaster could be worldwide and irreversible. An escaped micro-organism, capable of multiplying on its own, cannot be "cleaned up." But fortunately, we have the unprecedented opportunty, in the area of genetic engineering, to think about action before the technology has become a fait accompli.

Turning to the potential benefits of recombinant DNA technology, we hear of its potential medical value, for example, in the curing of genetic disorders. But let me point out that, of the 2,000 or so known genetic disorders, only a fraction can even be imagined to be amenable to treatment by procedures evolved from recombinant DNA technology. No single treatment is possible; each genetic disease is different and each would entail an individual and specific approach. Each would take time, effort, and a great deal of money. I should emphasize that the effort would be monumental.

The genetic disorders most commonly mentioned are blood conditions such as sickle cell anemia and certain types of thalessemia. You may have heard that immature blood cells might be taken from the bone marrow of a patient, and the cells kept alive in culture while introducing the correcting recombinant DNA into the cells. The so-called "cured" cells would then be injected back into the patient. This is not an appropriate forum for technical discussion, but I can assure you that the feasibility of such a procedure is highly speculative. There are about 1,500 newborns per year with each of these blood diseases—a small number when one considers the death rate due to cancer of all types. Since we do not have unlimited sources of funds it is clear that priorities have to be set. This is not an inhumane comment directed against those suffering from these relatively rare diseases, but a simple statement of reality. We can, however, find consolation in the fact that there are alternative medical procedures already under development for a number of these diseases.

I believe that it is unrealistic and irresponsible to dangle these and other hypothetical medical benefits before an unsuspecting public. We are witnessing the proverbial carrot on a stick. It is true that recombinant DNA techniques may accelerate our understanding of certain fundamental biological processes, and that this may help us understand what goes wrong when a cell becomes cancerous. We were already learning these things before recombinant DNA technology, and we can continue to do so. But with or without the new technique, no one has yet envisioned a rational, specific cure. Cancer is indeed a problem worth attacking, and the solution is right before our eyes:

It is prevention, not cure. One out of four of us in this room will die of cancer, and statistics show that most cancer deaths are due to chemical carcinogens which we ourselves are manufacturing. It is ironic that we are trying to justify a new technology—recombinant DNA technology—to overcome the unintentional ill effects of other technologies—the production of a variety of environmental pollutants. We seem to be bent on coexisting with our carcinogens rather than simply getting rid of them. We seem also to be intent upon ignoring the lessons of the past, which show that rushing into promising new technologies without adequate knowledge and evaluation of their consequences leads to new problems, and then to the frantic proliferation of more artificial panaceas and more problems.

One final word about benefits. You have heard that this technology may make possible the manufacture of rare drugs and industrial products from bacteria. I do not question that this will be feasible, and perhaps in the all too near future. Industrial firms all over the country are rushing into this profitable venture. It is possible that some of these potential products could result in true advances in our health and well-being. But one thing is worrying me. Who will decide when it is safe to release a specific recombinant organism, or when it can be grown in large quantities? On the basis of immediate benefits and quick profit, will General Electric release the bacteria—even if it isn't made by recombinant DNA; it doesn't matter—it is developing to destroy oilspills, only to find later that the ecology of the world's oceans has been irrevocably altered and many of its resources destroyed?

Mr. THORNTON. Are you suggesting that legislation, if it should be adopted, should deal not only with the release of information or results of recombinant DNA research, but also the results of all scientific research?

Dr. CAVALIERI. If they are in the category which is going to affect the environment; yes.

Mr. THORNTON. I just wanted to make that clear because you did add that to your original statement.

Dr. CAVALIERI. I added that because Dr. Cape reminded me that General Electric had not made this organism by recombinant DNA.

Mr. THORNTON. Thank you.

Dr. CAVALIERI. Should private industry be allowed to make decisions that could affect the entire Earth irreversibly? Should anyone make such decisions before all of our human resources, from all segments of society, have been brought to bear upon the questions?

I ask, perhaps with many of you, what is the rush? We have been through the arguments about the atom bomb and how it was essential that we build it before the Germans. But nothing urgent hangs on the results of recombinant DNA research. It is a new technique which excites a group of molecular biologists. They plan to use it as a tool for determining the structure and function of the DNA of animal and human cells. This would be a fair enough goal if we were not faced with uncertainties, the magnitude of which we cannot even sensibly guess. Even the most ardent proponents of the research agree that uncertainties do exist. My own view about the rush is that it is both psychologically and financially motivated. Recombinant DNA is an exciting tool, and scientists are bandwagon-

ers just like most other people. Industry, too, wants to get in on the ground floor. Competition is high both in industry and academia. Whatever the future impact of this technique may be, let us recognize the present facts. For one thing, research funds are easier to produce in this area, and in recent years we have all felt the crunch. In addition, like so many powerful new techniques, this one seems at first glance to promise knowledge, power, profit, and glory. No one wants to think of the long range.

Those of us who have opposed the precipitous rush into an area of research whose dangers can, however dimly, be perceived in advance, have spoken of the social responsibility of the scientist. That is, responsibility in the whole context of life, not just in the scientific sphere. But to many scientists, social responsibility seems to have the ring of antiscience or even of anti-intellectualism. They respond with cries about freedom of inquiry. I suggest that freedom of inquiry is not a first principle; it is not a law of thermodynamics. It has come to be treated that way, however, by the scientific community. This is not a defensible stand in the modern world, where science is often virtually an arm of technology. It is because biological science is just entering this era that birth pangs are so palpable. In my opinion, some of the proponents of recombinant research are they themselves antiscientific for they refuse to recognize the facts—a cardinal sin in scientific circles. They see their own aims and responsibilities as limited to the search for knowledge, ignoring the fact that their results provide the basis for industrial power and their choices will determine the directions of social change. They are thus inviting a public backlash against science in general, for the record of science-based technology in this century is not reassuring. I needn't mention the unforseen effects of thalidamide, DDT, and so on. The rush toward genetic engineering, without full consideration of all of its consequences, is an invitation to much greater disaster.

In that context, the awakening of public and governmental concern is certainly encouraging.

There are four bills before Congress at present. I hear there are several more now—H.R. 4759, H.R. 4232, S. 945, and H.R. 3191, which is the same as S. 621. Unfortunately, all these bills are inadequate, and I am opposed to them all in their present state. Two of them, as I understood them, simply make the NIH guidelines enforceable by law. Since the guidelines themselves are inadequate and do not even touch on the long-range issues, these bills would simply give the public a false sense of security.

The bill proposed by Representative Solarz, H.R. 4232, constitutes a better beginning since it aims to bring together various public representatives and specialists to reevaluate present laws and regulations relating to recombinant DNA research. However, the viewpoint is too narrowly concerned with immedate issues such as safety procedures.

Bill S. 945 proposes a commission which would carry out a broader study of the important questions raised by recombinant DNA research. The charge of the commission is laudable, but its value is negated by the proposed membership. The members are to be appointed by the Secretary of HEW with the advice of the National Academy of Sciences, and are to be drawn heavily from among

scientists actually engaged in recombinant DNA research. This is sheer conflict of interest. I believe very strongly that there should be a commission to study the long-range public issues arising from recombinant DNA research and from future developments in genetic engineering; but such a commission must not include any scientists or anyone connected with the scientific or industrial establishment. The exclusion of scientists, and so forth, from membership does not mean that they should not play an important role in supplying information to the commission, when requested.

But the final evaluations, which are ethical and social rather than scientific, must be made in a disinterested way by individuals who are qualified in those areas. An important role for such a commission would be to propose future decisionmaking mechanisms designed to protect not only the safety but also the freedom of the American people.

While such a commission is deliberating, it is only sensible that there should be a moratorium on interspecies recombinant DNA research. If, after the report of the commission to the Congress and to the President, it is decided that the research should proceed, my own view is that it should be confined to one or a very few high-security centers under Federal control. At these centers, research relevant to public safety—not to drug manufacture—should be the first order of priority so that we could decide more intelligently how or whether to proceed. We would be taking the calculated risk that foreign countries may proceed with less caution, thereby endangering all of us. But, more importantly, we would be providing the moral leadership which is so much needed in this area.

Thank you.

Mr. THORNTON. Thank you, Dr. Cavalieri, for your interesting presentation.

[The prepared statement of Dr. Cavalieri is as follows:]

STATEMENT TO BE READ BEFORE THE

CONGRESSIONAL SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY

March 30, 1977

I am a member of the Sloan-Kettering Institute for Cancer Research and a Professor of Biochemistry in the Graduate School of Medical Sciences of Cornell University. I have been involved in molecular biological research for 25 years but I am not now nor do I ever intend to carry on laboratory investigative work in the field of recombinant DNA.

You have heard Drs. Cape and Nathans extoll the virtues of recombinant DNA technology. I would emphasize that the only certain scientific benefit is a better understanding of DNA function in animal and human cells. You also have heard of the potential technological benefits - those involving the production of insulin, hormones and so forth. You have heard very little about the long-range applications of the technology and their possible bearing on human welfare, human freedom and human dignity. This is natural enough, since scientists and industrialists are not especially qualified to speak on these subjects. However, we all, as members of society, had better address ourselves to these questions very soon if we are to arrive at a sane solution to what is one of the greatest societal dilemmas of the 20th Century.

I will start by stating my position quite positively: I am opposed to recombinant DNA technology at present and until such time as adequate, enlightened and disinterested consideration and discussion has occurred among various groups including non-scientific professionals and the lay public. These and other recent hearings represent first attempts at sober discussion to be followed by deep reflection. As members of what I hope is still a respected community - the scientific community - I hope that we can make a contribution to your understanding of the problem. However, I believe that the final evaluations and decisions

must be made by society at large, and its representatives, rather than by scientists.

I will try to be as specific as possible in my commentary since I am sure you are all aware of and perhaps satiated with generalizations. First, concerning the probability of an accident. In the normal working day an investigator working with recombinant DNA proceeds step by step through literally hundreds of operations. To attach a probability value to a mishap in any one of these is to try to quantify human error - this is impossible. It can lead to no meaningful number. As you know, biological containment has been proposed by the NIH guidelines to minimize the dangers that could result from an accident. This means, at present, that a weakened strain of E. coli is used for recombinant DNA experiments. When these bacteria enter an inappropriate medium they are designed to commit suicide. They are expected to behave in this way if they enter the human intestinal tract, but the exact length of time required for the suicidal act there is not known, nor has it been established whether it may not sometimes be possible for these cells to transfer recombinant DNA to one of the many other types of healthy E. coli found there. If there were a transfer of DNA to these healthier bacteria the recombinant genes could then easily become part of the biosphere. The probability of this series of events is not known, but it must be taken seriously since even the most stringent physical containment facilities cannot exclude human beings with intestinal tracts, nor can they totally eliminate the possibility of accidents.

Another safeguard incorporated by the NIH guidelines is the specification that under certain conditions the more dangerous experiments involving recombination of DNA from unrelated species must utilize DNA fragments which have been identified and purified to the extent of 99%. Thus, few unknown

or dangerous genes would be present. In reality, however, it is not only very difficult to achieve this degree of purity, but it is essentially impossible to prove it in the case, say, of human DNA. The methods available are just not that refined. I emphasize, therefore, that the phrase "99% pure" is open to individual interpretation, and the guidelines thus create a feeling of safety which is not warranted.

In this connection, there is an even more disturbing and unpredictable factor which cannot even enter any of the hypothetical calculations for risk. This does not concern merely the physical purity of the DNA but, more importantly, its genetic purity. In the February issue of the journal Nature (261: 687 (1977)) an illustrious group at Cambridge, England, headed by Professor Fred Sanger, has reported a surprising new fact about the DNA of a bacterial virus. Up to the present each section of a DNA molecule was believed to contain the genetic information for a single protein. But these workers have shown that a pure DNA fragment, coding for a specific protein, may contain overlapping information that can also specify a second protein. If such a "pure" DNA fragment were used for recombinant DNA experiments, bacteria might be produced which could manufacture not only the desired product but also another, unexpected one which might be dangerous. The question of the purity of the DNA fragment in such an instance would be meaningless. The writers of the NIH guidelines did not bargain for this complication. I bring up this point to illustrate the fact that there are hidden traps everywhere - as any scientist will attest; it is axiomatic in science that such surprises are the rule rather than the exception. The discovery of overlapping genes by Professor Sanger and his colleagues represents not merely a new wrinkle in molecular biology but to my mind it emphasizes most vividly the certainty of uncertainty in an area where we can ill afford to take chances.

Dr. Halsted Holman, a professor of medicine at Stanford Medical School and a primary-care physician, has raised an interesting but disturbing problem. He notes that E. coli infections of the bloodstream cause a large number of deaths and that the incidence of infections is on the increase. He feels that three factors contribute to this situation:

1. increase in the elderly population requiring health care;
2. increased prevalence of chronic diseases;
3. increase in use of drugs which inhibit the immune response.

He notes, further, that "much research on recombinants is done in medical centers where there is considerable exchange between the people working in the laboratories and people seeing patients. Sometimes the same person does both. Thus we have a different epidemiological problem from the one envisioned in the guidelines. It is the problem of enfeebled bacteria interacting with persons whose resistance is compromised. It is a question of the epidemiology of infection of weakened human hosts with altered bacteria. Techniques for monitoring and controlling this situation are, at least to my knowledge, not well developed." Nonetheless, P3 and perhaps even P4 recombinant research facilities are now being built in many medical centers. This represents to me the height of irresponsibility.

I will conclude my commentary on accidental dangers by observing that a very low probability coupled to a high risk event leads inevitably to the area of value judgment. When this occurs we have a public issue which requires a political solution, not a scientific one. The low probability that a flame retardant would be confused with animal food was of no consolation to the large number of people in Michigan whose health and property were thereby damaged or destroyed. A nuclear disaster could affect millions of people and must be still more carefully guarded against, however low its probability. In the case of recombinant DNA technology we have even greater cause for concern, for a genetic disaster could be world-wide and irreversible. An escaped microorganism, capable

of multiplying on its own, cannot be "cleaned up." But fortunately, we have the unprecedented opportunity, in the area of genetic engineering, to think and take action before the technology has become a fait accompli.

Turning to the potential benefits of recombinant DNA technology, we hear of its potential medical value, for example in the curing of genetic disorders. But let me point out that, of the 2000 or so known genetic disorders, only a fraction can even be immagined to be amenable to eventual treatment by procedures evolved from recombinant DNA technology. No single treatment is possible; each genetic disease is different and each would entail an individual and specific approach. Each would take time, effort and a great deal of money. I should emphasize that the effort would be monumental.

The genetic disorders most commonly mentioned are blood conditions such as sickle cell anemia and certain types of thalessemia. You may have heard that immature blood cells might be taken from the bone marrow of a patient, and the cells kept alive in culture while introducing the correcting recombinant DNA into the cells. The "cured" cells would then be injected back into the patient. This is not an appropriate

forum for technical discussion but I can assure you that the feasibility of such a procedure is highly speculative. There are about 1500 newborns per year with each of these blood diseases - a small number when one considers the death rate due to cancer of all types. Since we do not have unlimited sources of funds it is clear that priorities have to be set. This is not an inhumane comment directed against those suffering from these relatively rare diseases, but a simple statement of reality. We can however find consolation in the fact that there are alternative medical procedures already under development for a number of these diseases.

I believe that it is unrealistic and irresponsible to dangle these and other hypothetical medical benefits before an unsuspecting public. We are witnessing the proverbial carrot on a stick. It is true that recombinant DNA techniques may accelerate our understanding of certain fundamental biological processes, and that this may help us to understand better what goes wrong when a cell becomes cancerous. We were already learning these things before recombinant DNA technology, and we can continue to do so. But with or without the new technique, no one has yet envisioned a rational, specific cure. Cancer is indeed a problem worth attacking, and the solution is already before our eyes: it is prevention, not cure. One out of four of us in this room will die of cancer, and statistics show that most cancer deaths are due to chemical carcinogens which we ourselves are manufacturing. It is ironic that we are trying to justify a new technology - recombinant DNA - to overcome the unintentional ill effects of other technologies - the production of a variety of environmental pollutants. We seem to be bent on co-existing with our carcinogens rather than simply getting rid of them. We seem also to be intent upon ignoring the lessons of the past, which show that rushing into promising new technologies without adequate knowledge

and evaluation of their consequences leads to new problems, and then to the frantic proliferation of/artificial panaceas and more problems. more

One final word about benefits. You have heard that this technology may make possible the manufacture of rare drugs and industrial products from bacteria. I do not question that this will be feasible, and perhaps in the all too near future. Industrial firms all over the country are rushing into this profitable venture. It is possible that some of these potential products could result in true advances in our health and well-being. But one thing is worrying me. Who will decide when it is safe to release a specific recombinant organism, or when it can be grown in large quantities? On the basis of immediate benefits and quick profit, will G.E. release the bacteria it is developing to destroy oil spills, only to find later that the ecology of the world's oceans has been irrevocably altered and many of its resources destroyed? Should private industry be allowed to make decisions that could affect the entire earth irreversibly? Should anyone make such decisions before all of our human resources, from all segments of society, have been brought to bear upon the questions?

I ask, perhaps with many of you, what is the rush? We have been through the arguments about the atom bomb and how it was essential that we build it before the Germans. But nothing urgent hangs on the results of recombinant DNA research. It is a new technique which excites a group of molecular biologists. They plan to use it as a tool for determining the structure and function of the DNA of animal and human cells. This would be a fair enough goal if we were not faced with uncertainties, the magnitude of which we cannot even sensibly guess. Even the most ardent proponents of the research agree that uncertainties do exist. My own view about the rush is that it is both psychologically and financially motivated. Recombinant DNA is an exciting tool, and

scientists are band-wagoners just like most other people. Industry, too, wants to get in on the ground floor. Competition is high both in industry and academia. Whatever the future impact of this technique may be, let us recognize the present facts. For one thing, research funds are easier to procure in this area, and in recent years we have all felt the crunch. In addition, like so many powerful new techniques, this one seems at first glance to promise knowledge and power, profit and glory. No one wants to think of the long range.

Those of us who have opposed the precipitous rush into an area of research whose dangers can, however dimly, be perceived in advance, have spoken of the social responsibility of the scientist. That is, responsibility in the whole context of life, not just in the scientific sphere. But to many scientists, social responsibility seems to have the ring of anti-science or even anti-intellectuallism. They respond with cries about freedom of inquiry. I suggest that freedom of inquiry is not a first principle; it is not a law of thermodynamics. But it has come to be treated that way by the scientific community. This is not a defensible stand in the modern world, where science is often virtually an arm of technology. It is because biological science is just entering this era that the birth pangs are so palpable. In my opinion, some of the proponents of recombinant research are themselves anti-scientific for they refuse to recognize the facts - a cardinal sin in scientific circles. They see their own aims and responsibilities as limited to the search for knowledge, ignoring the fact that their results provide the basis for industrial power and their choices will determine the directions of social change. They are thus inviting a public backlash against science in general, for the record of science-based technology in this century is not reassuring. I needn't mention the unforeseen effects of thalidamide, DDT, and so forth. The rush toward genetic engineering, without full consideration of all its consequences, is

an invitation to much greater disaster.

In that context, the awakening of public and governmental concern is certainly encouraging. There are four bills before Congress at present: HR 4759, HR 4232, S 945, and HR 3191 (which is the same as S 621). Unfortunately, all the Bills are inadequate and I am opposed to them all in their present state. Two of them, as I understand them, simply make the NIH guidelines enforceable by law. Since the guidelines themselves are inadequate and do not even touch on the long-range issues, these Bills would simply give the public a false sense of security.

The bill proposed by Rep. Solarz HR 4232, constitutes a better beginning since it aims to bring together various public representatives and specialists to re-evaluate present laws and regulations relating to recombinant research. However, the viewpoint is too narrowly concerned with immediate issues such as safety procedures.

The fourth bill, S 945, proposes a commission which would carry out a broader study of the important questions raised by recombinant DNA research. The charge of the commission is laudable but its value is negated by the proposed membership. The members are to be appointed by the Secretary of HEW with the advice of the NAS, and are to be drawn heavily from among scientists actually engaged in recombinant DNA research. This is sheer conflict of interest. (For example, the subtle influences which often prevent the NAS, in spite of its good intentions, from functioning fully in the public interest have been documented by Phillip Boffey in his recent book "The Brain Bank of America.") I believe very strongly that there should be a commission to study the long-range public issues arising from recombinant DNA research and from future developments in genetic engineering; but such a commission must not include <u>any</u> scientists or <u>anyone</u> connected with the scientific or industrial establishment. The exclusion of scientists

and so forth from membership does not mean that they should not play an important role in supplying information to the commission, when requested. But the final evaluations, which are ethical and social rather than scientific, must be made in a disinterested way by individuals who are qualified in those areas. An important role for such a commission would be to propose future decision-making mechanisms designed to protect not only the safety but also the freedom of the American people.

While such a commission is deliberating, it is only sensible that there should be a moratorium on inter-species recombinant DNA research. If, after the report of the commission to Congress and the President, it is decided that the research should proceed, my own view is that it should be confined to one or a very few high-security centers under Federal control. At these centers, research relevant to public safety - not to drug manufacture - should be the first order of priority so that we could decide more intelligently how or whether to proceed further. We would be taking the calculated risk that foreign countries may proceed with less caution, thereby endangering us all. But more importantly, we would be providing the moral leadership which is so much needed in this area.

Mr. THORNTON. In order to proceed and have some time for questions, I'm going to proceed immediately and recognize our final witness, Dr. David Baltimore, who is a Nobel laureate from the Center for Cancer Research, MIT, Cambridge, Mass. Dr. Baltimore shared his Nobel Prize with Dr. Howard Temin, of the United States, and Dr. Renato Dulbecco, of Italy, for work on human viruses, and has courageously discussed the potential applications of DNA recombinant techniques during the recent forum at the National Academy of Sciences.

We do have your prepared statement, Dr. Baltimore, which, without objection, will be made a part of the record. I would like to invite you to give your testimony at this time.

[A biographical sketch of Dr. Baltimore follows:]

CURRICULUM VITAE

DR. DAVID BALTIMORE

DATE AND PLACE OF BIRTH: March 7, 1938 in New York, New York.

CITIZENSHIP: U.S. Citizen SOCIAL SECURITY #110-28-4078

MARITAL STATUS: Married

EDUCATION:

1956-1960	Swarthmore College, Swarthmore, Penn. B.A. with High Honors in Chemistry, 1960
1960-1961	Massachusetts Institute of Technology, Cambridge, Mass., graduate courses toward Ph.D.
1961-1964	Rockefeller University, New York, New York Ph.D. received in 1964

MILITARY SERVICE: None

POSITIONS HELD:

1963-1964	Postdoctoral Fellow, Massachusetts Institute of Technology, Cambridge, Mass.
1964-1965	Postdoctoral Fellow, Albert Einstein College of Medicine, Bronx, New York
1965-1968	Research Associate, Salk Institute for Biological Studies, La Jolla, California
1968-1972	Associate Professor of Microbiology, Massachusetts Institute of Technology, Cambridge, Mass.
1972-present	Professor of Biology, Massachusetts Institute of Technology, Cambridge, Mass.
1973-present	American Cancer Society Professor of Microbiology
1974-present	Consulting Scientist in Medicine (Hematology and Oncology), Children's Hospital Medical Center, Boston, Mass. and Consulting Scientist in Pediatric Oncology, Children's Cancer Research Foundation, Boston, Mass.

HONORS: 1970 - First recipient of the Gustav Stern Award in Virology

1971 - Warren Triennial Prize from the Massachusetts General Hospital

1971 - Eli Lilly and Co. Award in Microbiology and Immunology

1974 - National Academy of Sciences' United States Steel Foundation Award in Molecular Biology

1974 - member of the National Academy of Sciences

1974 - member of the American Academy of Arts and Sciences

1974 - Gairdner Foundation Annual Award

1975 - Nobel Prize in Physiology and Medicine

EDITOR: 1971-1973 Journal of Molecular Biology

1969-present Journal of Virology

ADVISORY PANELS: 1969-1972 N.S.F. Advisory Panel for Genetic Biology

1971-1973 Cancer Research Center Review Committee of the National Institutes of Health

1973-1975 Cancer Special Program Advisory Committee of the National Institutes of Health

STATEMENT OF DAVID BALTIMORE, AMERICAN CANCER SOCIETY RESEARCH, PROFESSOR OF MICROBIOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASS.

Dr. BALTIMORE. Thank you, Mr. Chairman.

Let me first, before starting, correct one thing, which I know Dr. DulBecco would want me to correct. He's an American citizen, although born in Italy.

Mr. THORNTON. I appreciate that correction. Thank you.

Dr. BALTIMORE. I was initially part of a group of scientists who, in 1974, first drew attention to the potential problems inherent in the manufacture and study of recombinant DNA molecules. Since that time, I have been actively involved in discussions about the types of controls appropriate to this new methodology of modern biology.

Before considering the risks and benefits arising from recombinant DNA technology, I believe it is important to present the technique from within its historical context. Modern biology has been a very productive science but has progressed much more rapidly in the study of bacteria than it has in the study of higher cells, including those of human beings. Two considerations have led to the limited progress with higher cells: the large amount of genetic information in cells of higher organisms and the difficulty of carrying out genetic studies using higher organisms. Recombinant DNA technology has offered a partial solution to these problems of scale. The technology allows individual genes to be isolated away from all other genes and to be studied as independent entities. With this new technology, we have already gained new knowledge about the organization of the genetic material of higher cells and a treasure trove of new results can be expected as the technology receives wider application.

Further knowledge of the organization and function of genes in higher cells is of critical importance to our understanding of disease. The diseases which now plague the American population are mainly diseases in which cells malfunction. We do not understand the basis of the malfunction in any of these diseases and our ability to prevent and treat the diseases is limited by our knowledge of them. Recombinant DNA technology is a new tool in the continuing battle against our ignorance of how higher cells carry out their basic functions. It joins an impressive array of techniques developed over the last 30 years which have allowed biologists to see deeper and deeper into the functioning of cells. The goal of modern biology is the understanding of normal and aberrant living processes. We are very far from that goal in almost all critical areas of human biology but recombinant DNA methods should speed our acquisition of knowledge.

The new knowledge which will be acquired about the functioning of human and other cells will bring with it new capabilities. Because we do not know the shape of that new knowledge, it is impossible to specify what capabilities will be inherent in it. It is important to recognize that attempts to predict future developments in biology are severely limited by the meager knowledge we have of the biology of higher cells. Such terms as "genetic engineering" have little precise meaning because at present we can only use our imagination to guess the shape of the future and our imagination is extremely limited.

If we realize that recombinant DNA technology is only a tool of modern biology and is not a science in itself, then we also will realize that recombinant DNA technology by itself offers no benefits. It is the totality of modern biology which offers possibilities of benefit for the future and recombinant DNA methods are one, albiet a critical one, of the tools that the modern biologist can use. So an analysis of the benefits to come from recombinant DNA is like an analysis in 1940 of the benefits that might derive from the electron microscope. When the electron microscope was developed its powers were speculative—today we know that it has been a critical element in our increased understanding of both normal and diseased tissues.

The appropriate question is not what are the benefits to come from recombinant DNA technology but what are the benefits to come from modern biology *in toto*. The Congress of the United States has for many years strongly supported the notion that basic research in biology will bring with it critical understanding of those diseases that plague the citizens of the United States. The Congress has funded research without requiring specific justification for why one type of research will be more beneficial than another. This was a very farsighted policy of the Congress because it represented an understanding that it is impossible to predict with precision where critical advances in modern science will arise. An investigator working on a worm or a fly may come across a principle which is central to all of life and often such a principle will be more evident in a simple system than it will be within the context of the complicated biology of human beings. Biologists have devoted themselves to finding the truths of life and as part of that search biologists have developed the methods of recombinant DNA research which can allow modern biology to better attack problems of human cells.

What then are the benefits of basic research? They are, as they must be, entirely speculative. We believe that deeper knowledge of cancer will help to prevent it and cure it, but we cannot promise that that is true. We can, however, say with assurance that without new knowledge we will be extremely limited in our ability to prevent and cure cancer. It is very fashionable to say today that 80–90 percent of cancer has an environmental or lifestyle cause. From that fact certain scientists have made the facile conclusion that all we need do is search around in the environment and in our lifestyles to find the causes of cancer and so to allow their eradication.

One of the great men in the search for the causes of cancer has been Sir Richard Doll. In a recent article entitled "Strategy for Detection of Cancer Hazards in Man," he went through our present knowledge of the causes of human cancer and concluded:

> We cannot, of course, hope to detect hazards efficiently until we know how cancer is produced, so that a policy for detection must include the support of basic biological research. Success in this field is dependent on the development of ideas and is difficult to foster except by providing the conditions in which outstanding investigators are able to give free rein to their imagination.

I have that article here, if you wish to put it in the record.

Mr. THORNTON. We'll be pleased to receive it, and without objection we'll consider it for possible inclusion in the record.

Dr. BALTIMORE. Thank you very much.

[The article referred to is as follows:]

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review article

Strategy for detection of cancer hazards to man†

Sir Richard Doll*

Forty-four years ago, Sir Ernest Kennaway and his colleagues identified, for the first time, a pure chemical that was capable of causing cancer in animals, and a year later isolated another from material that was widespread in the environment. At that time, and even after these crucial observations, it was commonly assumed that cancers were an inevitable accompaniment of ageing and that little could be done to reduce the mortality they caused. It is now clear, however, that most, if not all cancers have environmental causes and can in principle be prevented. The identification of environmental hazards and clarification of the mechanisms through which they cause disease are thus among the highest priorities in cancer research.

SINCE Kennaway's seminal work[1,2], the evidence that cancer can be prevented has accumulated steadily and is now overwhelming. Whether it will ever be possible to prevent the disease altogether, as we can now prevent poliomyelitis and scurvy, is impossible to say until we know more about the mechanism by which it is produced; but we should be able to reduce the age-specific incidence rates—which account for a quarter of all deaths of men in Britain under 75 years of age—by at least 80 to 90%. That this is so, is suggested primarily by the great variation in the incidence of different types of cancer in different communities and in different parts of the world.

This variation is illustrated in Tables 1 and 2, which show maximum and minimum incidence rates for all cancers that are common enough somewhere for the disease to affect more than 1% of men or women by 75 yr, in the absence of other causes of death. The range of variation is never less than fourfold and is sometimes more than a hundredfold. I have presented the data as cumulative incidence rates up to 75 yr, despite the fact that rates at old ages tend to be unreliable where personal medical services are sparse, to illustrate how common some cancers can become in countries like our own where half the population lives to be over that age. In estimating the range of variation, however, I have limited comparison to ages under 65 yr.

With rare cancers, the very fact of their rarity makes the demonstration of their incidence in the small populations that have been studied outside the industrialised countries extremely difficult, if not impossible. Nevertheless, some clearly vary: for example, Burkitt's lymphoma, which never affects more than 1 in 1,000 people[3], varies at least 100-fold. Others, such as acute leukaemia in young adults and nephroblastoma in children, seem to be fairly constant everywhere.

Some of this variation is, of course, genetic in origin. That heredity is not the principal cause is, however, shown by migrant groups, whose experience of disease usually changes when they change their way of life in a new country, and by the variation in the incidence of cancer with time. The latter can seldom be demonstrated conclusively, partly because it is difficult to compare the efficiency of case finding at different periods, and partly because a high standard of case registration has obtained in only a few places for more than 10 yr—the most notable being Denmark and Connecticut, USA. We have, therefore, to rely to a large extent on trends in mortality, which may also be influenced by changes in the efficacy of treatment.

Nevertheless, some changes are so gross that it is impossible to doubt that there has been a real change in incidence: for example, the increase in lung cancer in all developed countries, the increase in oesophageal cancer in the black population of South Africa, and the decrease in gastric cancer in the USA. Many lesser changes have taken place in Britain during the last 20 years. These are shown in Table 3, which lists all those cancers for which the mortality rate, standardised for age, has changed by more than one per cent a year between 1958 and 1973. Several of these changes cannot be dismissed as artefacts, because the disease is easy to diagnose and the death rate has increased despite improving treatment (as with melanoma and cancer of the testis). Taken altogether, the evidence suggests that all common cancers have varied in incidence from time to time, just as they now vary from place to place.

Much of this variation can now be attributed to the action of specific agents. Indeed, so many are now known that we may reasonably hope to extrapolate from past experience in seeking others. I shall, therefore, begin by reviewing briefly the known agents and the ways in which they have been detected.

Iatrogenic hazards

About a score have been prescribed by doctors (Table 4). Most have caused only a few cases and their effect has been apparent to clinicians and pathologists because the microscopic appearance of the tumour or the site in which it occurred was so unusual. Examples include adenocarcinoma of the vagina in young women whose mothers had taken stilboestrol during the relevant pregnancy (recognised when a lift broke down in Boston and the paths of a gynaecologist and a pathologist crossed for sufficiently long for them to exchange experiences); angiosarcoma of the liver and spleen following the injection of thorotrast; squamous carcinoma of the thigh following the local application of coal tar ointment; squamous carcinoma of the

*Regius Professor of Medicine, University of Oxford.
†This article is based on the Sir Ernest Kennaway Lecture delivered at the Royal Institution on 11 November 1976.

Table 1 Range of variation in the incidence of common cancers in men (unless specified ♀)

Type of cancer	High incidence area	Cumulative risk by 75 years of age* (%)	Range of variation†	Low incidence area
Skin	Australia, Queensland	>20	>200	India, Bombay
Oesophagus	Iran, NE	20	300	Nigeria
Bronchus	England	11	35	Nigeria
Stomach	Japan	11	25	Uganda
Cervix uteri ♀	Colombia	10	15	Israel (Jewish)
Liver	Mozambique	8	70	Norway
Prostate	USA (black)	7	30	Japan
Breast ♀	USA, Connecticut	7	5	Uganda

*In absence of other causes of death.
†At ages 35–64 years.

palm of the hands associated with arsenicism; reticulosarcoma of the brain following immunosuppression to prevent rejection of a renal transplant; and a peculiar type of liver tumour in women using steroid contraceptives.

The only known agents in this group that have caused any substantial number of cancers have been ionising radiations, which probably caused between 5 and 10% of all childhood cancers in Western Europe and North America during the 1950s and 60s, when used for diagnosis during the pregnancy of the mother; and oestrogens, prescribed for post-menopause women, which may account for much of the recent increase in the incidence of endometrial cancer in the USA. In both cases, the risks were overlooked for a long time, because the tumours did not differ in any obvious way from the tumours that occurred quite commonly as a result of other causes, and they were eventually detected only after large scale case-control studies had been carried out with the object of investigating the role of the agents in the aetiology of the particular disease[7–9].

Despite the number of tumours caused by these last two agents, the total number of cases that are iatrogenic in origin is much less than readers of Illich's *Medical Nemesis* might suspect and cannot have constituted more than a minute proportion of the total impact of cancer on society.

Occupational hazards

Other agents have caused hazards in a wide variety of occupations. These are listed in Tables 5 and 6. In three instances the risks were discovered after the agents (4-aminobiphenyl, mustard gas and vinyl chloride) had been shown to cause cancer in animals. Other agents were discovered incidentally in the course of investigating other industrial hazards, as in the case of cancer of the prostate in cadmium workers and cancer of the lung in rubber workers. Most, however, were discovered because the interest of a clinician, an epidemiologist, or a pathologist was aroused by the observation of a cluster of cases that seemed too large to be easily attributable to chance. Sometimes these clusters have been quite small, as when Dr John Jones reported that he was disquieted to have seen two employees of the Mond Nickel Company develop nasal sinus cancer within a year. Often, however, the risk has been overlooked for a long time, particularly when the same type of cancer was common in the general population as a result of other causes.

Like the iatrogenic hazards, these occupational ones cannot have been responsible for more than a very small proportion of all cancers, as the total number of men who have been exposed in the course of their work, other than open air workers exposed to ultraviolet light and, to a lesser extent, the wide variety of workers exposed to asbestos, is small in proportion to the population as a whole. They are important, however, for two reasons.

First, they are important to the workers concerned who have had a 50% risk of developing the disease in some industries. Indeed, in one small group of 19 men employed on distilling 2-naphthylamine, the risk proved to be 100%, 18 dying of bladder cancer and the last having been killed in an accident shortly after the disease was diagnosed. Second, some of the agents concerned have found their way into the general environment, so that millions of people have been exposed to them unintentionally and sometimes in an uncontrolled way. These agents are listed in Table 6. It is easy enough to dismiss the corresponding risks on the grounds that the doses are minute; but we can no longer assume that thresholds exist for chemical or physical agents and we ought neither to ignore nor to condemn them until we have derived quantitative relationships between the dose to which individuals are exposed and the resultant incidence of the disease. At present we can do this only very crudely. Nevertheless, any quantitative evidence is better than none.

Industrial pollution

Consider, for example, polycyclic hydrocarbons and asbestos. For the first, we have evidence that the large amount of benzo(*a*)pyrene inspired by gas retort house workers produced a risk of lung cancer only about 80%

Table 2 Range of variation in the incidence of common cancers in men (unless specified ♀)

Type of cancer	High incidence area	Cumulative risk by 75 years of age* (%)	Range of variation†	Low incidence area
Colon	USA, Connecticut	3	10	Nigeria
Buccal cavity	India, part	>2	>25	Denmark
Rectum	Denmark	2	20	Nigeria
Bladder	USA, Connecticut	2	4	Japan
Ovary ♀	Denmark	2	8	Japan
Corpus uteri ♀	USA, Connecticut	2	10	Japan
Nasopharynx	Singapore (Chinese)	2	40	England
Pancreas	New Zealand (Maori)	2	5	Uganda
Penis	Uganda, part	1	300	Israel (Jewish)

*In absence of other causes of death.
†At ages 35–64 yr.

greater than the national average*. Since the residents of large towns are unlikely to have been exposed to more than one-hundredth of that amount—mainly from the combustion of domestic coal*—the contribution of these agents to the urban excess of the disease is unlikely to have been large, a conclusion that is confirmed by the low incidence of the disease in non-smokers irrespective of where they live.

As for asbestos, we know that it reaches the ambient air from a variety of sources, including the clothes of asbestos workers. These were presumably the principal source of exposure of the 37 men and women in nine countries who are reported to have developed mesothelioma of the pleura after being household contacts of asbestos workers[10]. The maximum concentration that has been found in the air near building sites where asbestos was being sprayed is, however, three orders of magnitude less than that which has been regarded as an acceptable concentration in the asbestos industry[11], and the amount that is commonly present in town air is still less by another two orders of magnitude. Unfortunately, we are still uncertain about the size of the risk that is associated with this accepted concentration of about 0.1 mg m^{-3}. In one study of an asbestos textile factory in England[12], it was found that the relative risk of lung cancer for men who had been employed for 20 yr decreased progressively from 10 times 'normal', if they had been employed for at least 10 years before 1933 (that is, the date when some control of asbestos dust in the air of factories first became effective in the UK), to 3½ times normal if they had been employed before 1933, but for less than 10 years, to 1¼ times normal if they had first been employed only after 1933. Few men who were first employed only after 1951 have yet been employed for 20 yr, but preliminary estimates (which are highly unreliable because the number of men observed is so small) suggest that some risk may still have persisted since that date. Detailed dust records were not obtained in the early years in a way that enables them to be compared with present data, but the amount of dust in the air was initially gross and continued to be much greater than at present for some time after 1933. Even in 1951, the mean dust level to which men were exposed is likely to have been 3½ times greater than it is now, and we shall have to wait for many years before industrial data enable us to make a reasonable estimate of the possible risk associated with an average exposure up to 0.1 mg m^{-3} during normal working life.

Measurements like these exculpate individually as major contributors to the gross variation in cancer incidence between countries all the agents that are known to cause specific occupational hazards (other than ultraviolet light), whether acting within industry or as pollutants in the general environment. In so far as we can explain this variation, it seems rather to be due to differences in social behaviour, diet and the opportunity for infection.

Table 3 Changing mortality rates from different cancers* (England and Wales, 1958 to 1973)

Type of cancer	(%) Change Males	Females
Melanoma	+95	+47
Myelomatosis	+65	+70
Lung	+29	+94
Pancreas	+19	+20
Testis	+19	
Oesophagus	+16	+17
Stomach	−25	−34
Buccal cavity	−38	−24
Cervix		−23

*All cancers with rate of change equal to or more than 1% per year.

Table 4 Iatrogenic causes of cancer

Agent	Site of cancer
Diagnostic or therapeutic X rays	All sites
Thorium	Bone
Thorotrast	Liver, spleen marrow (leukaemia)
Polycyclic hydrocarbons in coal tar ointments	Skin
Alkylating agents	
Melphalan, cyclophosphamide	Marrow (leukaemia)
Oestrogens	Endometrium, breast (M) ? breast (F)
Stilboestrol (transplacental)	Vagina
Steroid contraceptives	Liver
Androgens (anabolic steroids)	Liver
Arsenic	Skin, lung
Chlormaphazine	Bladder
Immunosuppressive drugs	Reticulosarcoma
Phenacetin	?Renal pelvis

Other hazards

The other agents that are known to cause cancer are listed in Table 7. The number is small, but the cancers that have been produced are legion. Cancers of the buccal cavity attributable to chewing, for example, account for a quarter of all cancers in men in parts of India, while cancers of the lung attributable to smoking account for more than a third of all lethal cancers in men in Britain.

One agent, aflatoxin, was discovered to be a powerful carcinogen as a result of an outbreak of poisoning that killed 100,000 ducks and turkeys in British farms. The outbreak was traced to a consignment of peanut meal contaminated with *Aspergillus flavus* which produced a metabolite that not only caused acute liver failure in poultry, but also caused cancer of the liver in minute doses in a wide variety of animals[13,14]. Human liver cells contain the enzymes necessary to produce the active agents (the epoxy-metabolites of aflatoxin), and *Aspergillus flavus* is a frequent contaminant of foodstuffs stored under hot and humid conditions. Now it has been shown that the incidence of liver cancer in Thailand, Singapore, Kenya, Swaziland and Mozambique is proportional to the amount of aflatoxin in the diet[15,16]. The vagaries of daily diet make it unlikely that we shall ever be able to establish the relationship in individuals; but the total evidence is strong enough to justify an attempt to prevent the disease by reducing exposure. Unfortunately, this will not be easy, as fungal contamination is difficult to avoid under the conditions in which the staple foods are commonly stored in the tropics, and it will be expensive to substitute alternative methods.

The other agents listed in Table 7 were, for the most part, discovered as a result of clinical acumen dating back

Table 5 Occupational causes of cancer not contributing to general environmental pollution

Agent	Site of cancer
Ultraviolet light	Skin
Aromatic amines	Bladder
2-naphthylamine	
1-naphthylamine	
Benzidine	
4-aminobiphenyl	
bis-chloromethyl ether	Bronchus
Benzene	Marrow (leukaemia)
Mustard gas	Bronchus
	Larynx
	Nasal sinuses
(Nickel ore)	Bronchus
	Nasal sinuses
(Chrome ore)	Bronchus
Cadmium (?)	Prostate
Agents in isopropyl oil hardwood furniture manufacture / leather goods manufacture	Nasal sinuses

Table 6 Occupational causes of cancer contributing to general environmental pollution

Agent	Site of cancer
Ionizing radiations	Bronchus Skin Bone Marrow (leukaemia)
Polycyclic hydrocarbons in soot, tar, and oil	Skin, scrotum
Arsenic	Bronchus Skin
Asbestos	Bronchus Pleura, peritoneum
Vinyl chloride	Liver (angiosarcoma)

nearly 200 years to Soemmerung's description of lip cancers in pipe smokers[17]. Clinical associations, however, tend to be overlooked if the conclusions suggested are socially unacceptable, and little attention was paid to the possible effects of smoking until the death rate from lung cancer in men had increased 25-fold (Fig. 1). The conference that was called by the Medical Research Council in 1947 could not decide whether the increase was real or an artefact due to improved diagnosis, but it did recommend a study to seek a possible cause. The subsequent enquiry showed that patients with lung cancer tended to smoke more than other patients, and within 3 years it was possible to conclude from the human evidence alone that cigarette smoking was a cause of the disease[18]. Whether these observations, or any others that are both practicable and ethical to obtain, can be regarded as constituting logical proof that a carcinogenic agent has been detected is debatable and is not of great interest. What is of interest is whether the evidence justifies an attempt at prevention and, if so, whether removal of the agent is followed by the result we seek[19].

Prevention should, of course, ideally be carried out in a controlled way with random allocation of individuals, or groups of individuals, to experimental and control series. In practice, however, this is seldom possible as the experiment is likely to require the cooperation of a large number of people who have to be convinced that it will be successful before it can be begun. Everyone, therefore, will want to be in the experimental group. This is what has always happened in industry; but when the disease disappears, as so many occupational cancers have, few people have challenged the logic that led to the intervention.

Once smoking began to be studied seriously as a cause of cancer, data were soon collected that confirmed the old clinical observation of a relationship with cancer of the mouth, and there are now strong grounds for believing that it also causes many cancers of the pharynx, larynx and oesophagus. Weaker, but consistent, evidence—like that summarised in Table 8—also suggests that it may play a part in producing cancers of the bladder and pancreas.

That alcohol contributes to the causation of a large proportion of cases of cancer of the oesophagus, and to a somewhat smaller proportion of cancers of the mouth, pharynx and larynx, in some countries, has been suspected ever since the mortality from these cancers was found to be unusually high in publicans, waiters and others employed in alcoholic trades[24]. The subject has, however, proved so unattractive to research workers that we still do not even know whether it is the alcohol itself that is responsible (possibly by solubilising a specific agent) or whether it is another component of alcoholic drinks that may vary in amount from one drink to another. That the subject has been unpopular may have been because pure alcohol is not carcinogenic to laboratory animals or because the amount consumed by the individual is difficult to assess with accuracy—or even because of a natural aversion for investigating such an unpopular subject. Interest in it has, however, been revived and studies are now being carried out on oesophageal cancer in parts of France where the characteristic alcoholic drinks are cider and cider-based liqueurs[25]. If, however, alcoholic drinks are important in the aetiology of cancers of the upper digestive tract in Europe and North America, they certainly do not explain

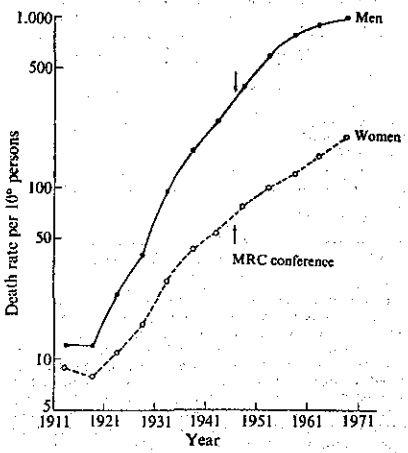

Fig. 1 Trend in crude death rate from lung cancer 1911–1971, by sex, showing state at time of MRC conference.

the astronomical figures for the incidence of the disease in central Asia, where very little alcohol is consumed.

Viruses

Another potential hazard is infection with an oncogenic virus, but it is still an open question whether viruses can ever cause cancer in man. Direct evidence of case-to-case infection is extremely weak—no-one, for example, who has used adequate controls has been able to repeat Vianna, Greenwald and Davies's[21] observation that patients with Hodgkin's disease have had unusually close personal contact —and the laboratory evidence that cancers are associated with viral infection is open to several interpretations.

Table 7 Other environmental causes of cancer

'Agent'	Site of cancer
Sunlight	Exposed skin (rodent ulcer, squamous carcinoma, ? melanoma)
Associated with use of 'Kangri' and 'dhoti'	Skin of abdomen, groin, and thigh (squamous carcinoma)
'Reverse smoking'	Palate
Chewing betel, tobacco, lime	Mouth
Smoking	Mouth, pharynx, larynx, bronchus, oesophagus, bladder, ? pancreas
Aflatoxin	Liver
Schistosomiasis	Bladder
Associated with sexual intercourse	Cervix uteri

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Table 8 Risk of death from cancer of pancreas in continuing cigarette smokers relative to life-long non-smokers (prospective studies)

Population*	Sex	Risk compared with that in non-smokers				
		Cigarette smokers	Current cigarette smokers smoking per day			
			1–9	10–20	21–39	40 or more
US citizens (77)	F	1.8				
(108)	M	2.7				
US veterans (493)	M		0.9	1.9	2.2	1.9
Canadian pensioners (89)	M		1.4	2.0	2.4	
Swedish random sample (46)	M		1.6	3.4	5.9	
British doctors (92)	M		1.4	1.4	2.1	

*Numbers of deaths in parentheses: for details see Hammond[20], Kahn[21], Department of National Health and Welfare[22], Cederlof *et al.*[23] and Doll and Peto[19].

Consider, for example, the extensive evidence that now connects the EB virus with Burkitt's lymphoma and carcinoma of the nasopharynx. In epidemic areas these diseases occur nearly always in individuals infected by the virus. Viral DNA is present in all the tumour cells and determines the expression in them of virus-coded neoantigens; and virus production can be activated in some of the tumour cells in the laboratory. The EB virus is widespread in human society and is the cause of infectious mononucleosis, when it stimulates the proliferation of mononuclear cells of the lymphatic series. *In vitro*, it confers the property of continuous growth on normal human B lymphocytes in culture, in a way that is analogous to malignant transformation. Finally, it has been shown to cause malignant lymphomas in South American cotton top marmosets on experimental inoculation.

What more can laboratory investigation be expected to do? The International Agency for Research on Cancer[26] is attempting to relate the development of the disease to new infection by following up children in the West Nile district of Uganda from whom blood samples have been taken for serum studies; but the results are unlikely to be decisive if, as one suspects, viral infection is only one of several conditions necessary for the development of the disease. If this turns out to be so, the only remaining approach will be to develop a vaccine that can be shown to prevent the disease[27] —immensely difficult though that must be—and the same would also be true if cervix cancer were firmly linked to infection with the type II herpes simplex virus or to any other infective agent.

That cervix cancer is venereal in origin is now virtually certain. We know that the disease spares nuns and is most common in prostitutes; that the risk increases with the number of marriages and with the age at which coitus first occurs, but not with the number of pregnancies, nor with the frequency of intercourse within marriage; and that more of the husbands of affected women have had extramarital intercourse than of the husbands of control women[28–30]. To these facts we can add Beral's observation[31] that the mortality from cervix cancer in cohorts of women of different ages varies with the incidence of gonorrhoea at the time they were 20 years old, and the accumulating evidence that obstructive methods of contraception are protective[32].

Interaction of agents

If viruses do, in fact, cause cancer, they may do so only by interacting with other factors, and this may account for the separate correlation of hepatitis B antigen and aflatoxin with hepatoma and of the EB virus and gross malarial infection with Burkitt's lymphoma. That two different agents may interact to produce cancer has been established by occupational studies which have demonstrated interactions between smoking and asbestos and smoking and ionising radiations and have provided quantitative data like those on the incidence of lung cancer in uranium miners in the USA[33].

Similar data are now also being obtained by the International Agency for Research on Cancer[34] for the interaction between tobacco and alcohol in the production of oesophageal cancer in France. Preliminary estimates, based on a retrospective case-control study of patients and a random sample of the population, suggest that the risk of developing the disease increases both with the amount smoked and with the amount drunk, until among men who drink 8l or more grams of ethyl alcohol (equivalent to 7 whiskies) and smoke 20 or more cigarettes a day, the risk is 45 times that in those continent men who drink less than 40 grams and smoke less than 10 cigarettes a day.

The existence of such interactions, which has been suspected since the early experiments of Rous and Kidd[24] and Berenblum and Shubik[25], can be of great importance. For they may provide not only the explanations for apparently conflicting observations, but also alternative means of preventing disease, one of which may be more practicable than the other. If, for example, smoking and asbestos interact to produce bronchial cancer, there may be no point in trying to give quantitative labels to their respective shares. Both may be responsible for producing more than half the cases in the sense that the elimination of either would reduce the total risk by more than 50%. The important conclusion is that we can break the chain of causation at either of two links, and it may be as idle to try and partition responsibilities as it is to try to quantify the relative contributions of nature and nurture to disease in general.

Strategy for detection

In this incomplete review, I have sought to provide an account of the hazards of cancer to man and to use the experience of the past to indicate how other hazards can be detected in the future. We cannot, of course, hope to detect hazards efficiently until we know how cancer is produced, so that a policy for detection must include the support of basic biological research. Success in this field is dependent on the development of ideas and is difficult to foster except by providing the conditions in which outstanding investigators are able to give full rein to their imagination.

Test of products before use

Two types of hazard stand out as socially unacceptable, although they are relatively unimportant numerically: that is, the hazards associated with occupation and the use of prescribed drugs. The evidence that chemical carcino-

gens, or their reactive metabolites, are commonly electrophilic, react with DNA and, in consequence, are able to induce mutations, has suggested that it may be possible to predict carcinogenicity by relatively quick and simple tests with bacteria. It is not certain that any one test, or combination of tests, will prove to be adequate, but preliminary results are encouraging[38].

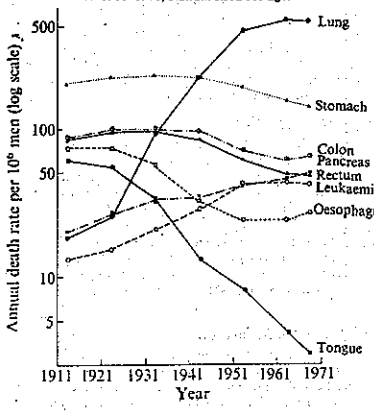
This, however, will not absolve us from making arrangements to detect hazards to man. Not only must we expect some chemicals to escape the net, particularly if they are hormones or act as promoters, enzyme inducers, or repair inhibitors; but we shall also wish to use some, and possibly many, substances that give positive results in animals, if the benefits are judged to be great enough to outweigh the harm. The continuing challenge to laboratory scientists is to discover enough about metabolism and the mechanisms of carcinogenesis in man to enable us to predict the extent of the hazard if the substance is used in a particular way. Meanwhile, we must either refrain from introducing such immensely useful materials as phenobarbitone, isoniazid, DDT, saccharin, and the minute amounts of stilboestrol that are used to fatten cattle, although they do not have any detectable effect in man, or arrange to detect and quantify hazards to man at the earliest opportunity.

Record linkage

Embryo mechanisms suitable for this purpose already exist in Britain, that are based on the records of the National Health Service and the Office of Population Censuses and Surveys, and to a varying extent in other countries[37–40]. Identifying information about all people who develop cancer is already integrated into a single file in England and Wales, and we now need to create similar files of people who are exposed to different chemicals. The Registrar-General has begun to do this by maintaining a file of a 1% sample of the population which is up-dated at each successive census in respect of births, deaths, immigrants and emigrants, and by recording the cumulative occupational experience of the selected sample throughout their lives. This file can be linked within OPCS to the occurrence of cancer and so can provide an automatic assessment of the risks associated with any particular industry. It will be necessary, however, to increase the size of the sample to at least 10% before it will be of any value for any but the larger risks. Very little information is included about specific exposures and it will probably also be necessary to require industry to maintain records of all employees who are exposed to new chemicals, so that they can be checked periodically against the file of cancer cases. Similarly, if we are serious in our desire to control adverse reactions to drugs, including reactions like cancer which occur only infrequently or after a prolonged latent period, we shall have to introduce some system for recording drug usage such as Skegg[41] is now doing on a pilot scale in 20 practices, or possibly create a new category of drugs that can be prescribed only on special forms for a period after they are introduced. Data that identify the patients can then be stored in a computer for subsequent matching with similar data in the cancer index.

The concept of linking records by computer has given rise to anxiety lest they are used to the detriment of the individual, as has happened when personal records have been linked by credit organisations in the USA, and some doctors have been worried by the apparent loss of confidentiality. Confidentiality can, however, be protected in a computer much more easily than in the standard case-note, and I know of no instance where the provision of personal information to a bona fide medical research worker has been abused. It is, of course, for the public to decide; but in my experience, most people understand that we cannot protect them against disease unless we are allowed the necessary tools. Record linkage of the type required is, moreover, not expensive when the essential records have to be made for other purposes, as they now all are—the only defect of the present system being that the records are not organised in a way that enables them to be used to detect hazards to health.

Fig. 2 Trends in mortality from common cancers in men 1911–1971, standardised for age.



Cancer incidence and mortality rates

Record linkage is less useful as a means of detecting hazards arising from environmental pollution or household materials, if there is no greater human exposure at the source of their creation or manufacture. In these circumstances we can rely only on cancer and death registries to arouse suspicion by revealing changes in the incidence of disease with time or place. Such registries are, also, one of our principal weapons for obtaining clues to other hazards that are not iatrogenic, occupational or attributable to pollution and which account for the mass of cancers that fill our hospitals today. Death rates for most of these and other cancers that were common between 1911 and 1970 are shown in Figs 2 and 3. The rates have been standardised for age and are limited to ages under 65 years, as diagnostic services for old people were so much less effective in the earlier part of the period. All the trends must have been affected by changing diagnostic standards and many will also have been affected by improving treatment, but we cannot avoid the conclusion, which accords with clinical experience, that cancers of the stomach, colon and rectum, and cancers of the breast and uterus (though not of the ovaries) have been common for many years so that if they are environmental in origin, as the evidence of geographical and social variation suggests, the responsible factors must have been prevalent at least before the beginning of the century.

Investigation of diet

One feature of the British way of life that has distinguished it from the Asiatic or African way for the appropriate length of time is its diet, and factors related to diet have been suspected of contributing to the production of cancer for many years. Until recently, however, there has been little precise evidence and very few promising ideas. Now, a spate of fresh ideas enables dietary factors to compete for the interest of research workers on almost equal terms with

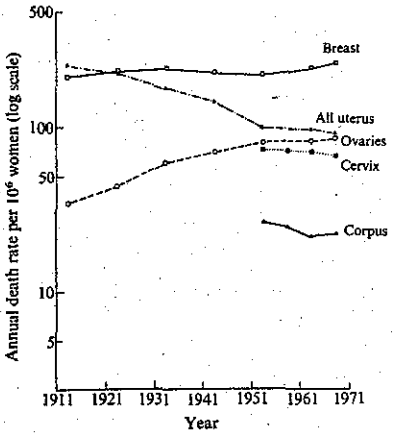


Fig. 3 Trends in mortality from common cancers of breast and genital tract in women, 1911–1971, standardised for age.

viruses and immune reactions. One such idea, to which I referred previously, was that aflatoxin might be responsible for tropical liver cancer. Another was the discovery that the cycad nut contained a constituent (cycasin) that was harmless in itself, but which gave rise to a carcinogen in the bowel of an animal with a normal intestinal flora. This was not fruitful in itself, but it focused interest on the possible role of intestinal bacteria and led Williams to examine the intestinal flora of people living in areas where the incidence rates of colon cancer were grossly different. Populations with a high risk were found to be characterised by the presence in their faeces of large numbers of anaerobic bacteria that were able to dehydrogenate bile acids, and Williams and his colleagues postulated that this might result in the production of carcinogens that acted locally on the colonic mucosa[41]. In 1975, Meade and his colleagues at Northwick Park, working in conjunction with Williams' group, reported the preliminary results of a retrospective study of patients with and without large bowel cancer which supported this idea[42], and these findings have now been confirmed in twice as many patients[43]. The original hypothesis will, however, have to be elaborated if it is to account for the low incidence of the disease in Finland and the increased incidence in the upper socio-economic classes in Hong Kong[32,44]; and Hill[45] suggests that it may also be necessary to have a high level of vitamin K to act as a hydrogen acceptor, before carcinogens can be formed under anaerobic conditions in the gut.

Burkitt's[46] hypothesis, that the relative lack of indigestible fibre in the diet of industrialised countries might be the primary cause of a variety of diseases of the large bowel that are absent in populations whose diet consists of natural unprocessed foods has also opened up new lines of thought. The greater bulk of faeces and the more rapid transit time associated with a high fibre diet could hardly account in physicochemical terms for the sort of gross differences in the incidence of large bowel cancer that occur between black African and the English-speaking countries; but the altered conditions in the bowel might perhaps account for the variation in the intestinal flora.

A fourth way in which diet may affect the incidence of cancer is by providing the raw materials from which nitrosamines are produced in the stomach—a group of powerful carcinogens that are still looking for human cancers to induce. Potential carcinogens of this group can be formed in acid gastric juice by the action of nitrites on secondary amines in food—the nitrites being present because of their use as preservatives, or because they were formed from nitrates in the mouth as a result of bacterial metabolism. This, however, is speculative. All we know for certain is that gastric cancer was common in the relatively poor populations of northern Europe and Japan (though not in most of the even poorer populations of Africa), that it has been becoming progressively less common in Western Europe and much less common in the USA, that it is less common in Japanese migrants to California and Hawaii than in the Japanese in Japan, and that the disease in the migrants tends to occur in those who eat pickled vegetables and dried and salted fish and not in those who eat such Western vegetables as tomatoes, celery, corn, lettuce and onion[44]. Could this be, as Weisburger and Wynder[47] suggest, because the small amounts of vitamin C inhibit the formation of nitrosamines in the stomach? Alternatively, it may be that the progressive reduction in incidence is due to better preservation of food, with a consequent reduction in the opportunity for bacterial or fungal contamination.

That vitamins may play a part in protecting against cancer is also suggested by experiments[48] on animals in which the incidence of cancer was reduced by a vitamin A-enriched diet. Now two sets of human data—one a prospective study of men with known dietary histories[49] and another a biochemical investigation of serum A levels in patients and controls[50], suggest that a deficiency of vitamin A may increase the risk of squamous cell carcinoma of the bronchus in cigarette smokers.

Fat also is a possible factor. Its consumption is closely correlated with the incidence of colon cancer ($r=0.78$) and breast cancer ($r=0.79$) in different countries, and several investigators have suggested that its content in the diet may directly affect the incidence of these diseases[51–53]. Armstrong[53] recently pointed out that the incidence of endometrial cancer was even more closely correlated with dietary fat ($r=0.85$) and showed that excess consumption of fat could account for five of the clinical characteristics that tend to be associated with the development of this disease: that is, obesity, early menarche, late menopause, maturity onset diabetes, and hypertension. Virtually all oestrogen produced in post-menopausal women is derived from oestrone which, in turn, is produced by aromatisation of the androstenedione secreted by the adrenals. Fat could play a part either because androstenedione is converted to oestrone in adipose tissue[54] or, perhaps, by inducing the oxidase systems that metabolise pre-carcinogens.

Conclusion

I have concluded by referring to some of the hazards that may be associated with diet, not because I believe that their existence has been proved, but because they provide an indication of the way in which the hazards that are responsible for the majority of human cancers may be detected in the future; that is, by a combination of epidemiological and laboratory enquiries. Such studies were often conducted independently in the past, with very little contact between the research workers involved. The position was, however, transformed when the World Health Organization set up the International Agency for Research on Cancer with the explicit purpose of encouraging such collaboration internationally, and it has been further strengthened in this country now that the Cancer Research Campaign, the Imperial Cancer Research Fund and the Department of Health and Social Security have joined the Medical Research Council in establishing academic units of cancer epidemiology within, or in close association with, the major departments of basic cancer research. With this collabora-

tion, a rational use of medical records, and continued support for general biological research. I see no reason why causes for the remaining common cancers should not be detected within one or two decades. That is not to say that it will be easy to prevent the disease. For if, as I suspect, these hazards are associated with the common diet of developed countries, the problems that we are now having to face in preventing tobacco-induced cancer will seem childishly simple.

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articles

Rapidly-formed ferromanganese deposit from the eastern Pacific Hess Deep

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A thick ferromanganese deposit encrusting fresh basaltic glass has been dredged from the Hess Deep in the eastern Pacific. Contiguous layers within the Fe-Mn crust have been analysed for uranium-series isotopes and metal contents. The rate of accumulation of the deposit, based on the decline of uranium-unsupported ^{230}Th, is calculated to be approximately 50 mm per 10^6 yr. Based on hydration-rind dating of the underlying glass and an 'exposure age' calculation, this rate is concluded to be too slow, and an accretion rate on the order of 1 mm per 10^3 yr is more consistent with our data.

INDURATED metal-rich crusts associated with probable hydrothermal areas on the seafloor have been reported[1–4]. Ferromanganese encrustations, sampled on active spreading centres, include those from the Mid-Atlantic Ridge, sampled during the Trans-Atlantic Geotraverse (TAG) expedition[2,3] and during the FAMOUS project[1], from the flank of a seamount at the crest of the East Pacific Rise[1], and from the Galapagos Spreading Center[4]. These deposits have been attributed to precipitation from hydrothermal fluids which gained high metal contents during interaction of seawater with basaltic rock at elevated temperatures. Although not conclusive, this type of genesis is more consistent with the geochemical and geological evidence than is a diagenetic formation by metal remobilisation and subsequent precipitation within sediment or formation by direct precipitation from seawater. Experimental evidence[5,6] showing that seawater becomes greatly enriched in Fe and Mn during interaction with fresh basalt at elevated temperatures seems to support the hydrothermal origin.

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Dr. BALTIMORE. So the leading investigator of the causes of cancer believes that more basic research is necessary before those causes can be found. Recombinant DNA research is a critical tool in the development of basic research knowledge which can help in finding new methods for prevention and cure of cancer.

You notice that I am not speculating about any precise benefits which could come from recombinant DNA work. It is the nature of basic research that we cannot know what it will find and therefore there is no way to precisely define the benefits it will bring. But if you believe, as I believe, that with knowledge comes new capabilities, then basic biological research is likely to bring us new capabilities to handle the diseases which plague us.

RISKS OF RECOMBINANT DNA RESEARCH

There are two basic types of risks which one must take into account in considering whether recombinant DNA techniques present a hazard. One is the risk of the misuse of the knowledge that can be provided by the techniques, and the other is the risks of specific damage that can be produced by the use of the techniques themselves. I should like to deal with these two risks separately.

The possibility of misuse of the knowledge that can be derived from recombinant DNA research is a part of the general problem of the misuse of the techniques of modern biology. Two general categories of potential misuse are often distinguished: One is in the development of biological warfare weapons and the other is in the development of methods of genetic engineering.

I believe that it is very important to strengthen the interpretation of the Biological Warfare Convention of 1975 which has been given by the Arms Control and Disarmament Agency. They have concluded that the Biological Warfare Convention bans the use of recombinant DNA techniques for the development of biological weaponry and if that interpretation is internationally recognized it will go a long way towards preventing the use of recombinant DNA methods in the development of weapons. Again, I have with me, if you wish to put it in the record, the correspondence between myself and the Arms Control and Disarmament Agency in which that is made explicit.

Mr. THORNTON. Without objection, we will receive it, subject to the same criteria as previously noted.

Dr. BALTIMORE. Thank you.

[The information to be provided is as follows:]

JUL 9 1975

UNITED STATES ARMS CONTROL AND DISARMAMENT AGENCY
WASHINGTON, D.C. 20451

July 3, 1975

Professor David Baltimore
Massachusetts Institute of Technology
Center for Cancer Research
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Dear Professor Baltimore:

Dr. Ikle has requested that I respond to your letter of May 22, 1975, in which you raise the question as to whether the Biological Weapons Convention prohibits production of recombinant DNA molecules for purposes of constructing biological weapons. In our opinion the answer is in the affirmative. The use of recombinant DNA molecules for such purposes clearly falls within the scope of the Convention's provisions.

I am enclosing, for your information, a copy of the transcript of the hearing before the Senate Foreign Relations Committee. You will note that the Committee shared your concern about the scope of the Convention, as evidenced by the following question, appearing on p. 29:

> "Question 15. Would the Biological Convention prohibit future types of biological warfare which might employ techniques beyond the current "state of the art", for example, some means of altering the structure of genes so as to modify behavior?"

ACDA responded that: "The Biological Weapons Convention would prohibit any future type of warfare which employed biological agents or toxins, regardless of whenthe agent or toxin was first developed or discovered. This also applied to weapons, equipment and means of delivery. In other words, the Convention prohibits not only existing means of biological and toxin warfare but also any that might come into existence in the future."

This interpretation is based upon the negotiating history as well as the explicit language of the Convention, and, we believe that it is shared by the other signatories.

Sincerely,

James L. Malone

James L. Malone
General Counsel

Enclosure:
As stated.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

CENTER FOR CANCER RESEARCH

77 MASSACHUSETTS AVENUE, CAMBRIDGE, MASSACHUSETTS 02139

May 22, 1975

Dr. Fred Ikle
United States Arms Control
and Disarmament Agency
Washington, D.C. 20451

Dear Dr. Ikle:

I am writing to you on behalf of the American members of the "Organizing Committee for an International Conference on Recombinant DNA Molecules", a committee of the Assembly of Life Sciences of the National Research Council.

It has become evident recently that a new technique of molecular biology, the ability to construct recombinant DNA molecules, could allow the design of new biological agents combining characteristics from different organisms. The potential for creation of new agents of biological warfare is inherent in this technology. At the recent Conference on Recombinant DNA Molecules in Asilomar, California, this question was not discussed because we were more concerned about the potential public health consequences of current research using this methodology.

Now that the Asilomar Conference is behind us, we have become concerned whether existing International treaties cover the use of modern techniques of biology to design new weapons of war. Specifically, we wish to know if the Biological Weapons Convention is relevant. Because the Convention appears to ban any developmental work on biological weapons, it would seem to ban use of recombinant DNA technology for such purposes. I refer to Article I which says:

> Each State Party to this Convention undertakes never in any circumstances to develop...microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

My question to you is whether it would be United States policy that Article I prohibits production of recombinant DNA molecules for purposes of constructing biological weapons. I also wonder whether you would see any reason why other signatories would not interpret the Convention in a similar fashion.

For your information the names and addresses of the other American members of the Committee are given below:

Dr. Paul Berg, Department of Biochemistry, Stanford University, School of Medicine, Stanford, California (Chairman of the Committee)

Dr. Maxine Singer, Laboratory of Biochemistry, National Cancer Institute, Bethesda, Maryland 20014.

Dr. Richard Roblin, Infectious Disease Unit, Massachusetts General Hospital, Boston, Mass.

Sincerely,

DB/mts

David Baltimore
American Cancer Society
Professor of Microbiology

Dr. BALTIMORE. Genetic engineering is a phrase which covers two types of possible activities. One is the use of genes to provide therapy for an individual who is suffering from a disease caused by a genetic defect. Such a procedure could lead to the amelioration of the symptoms of the disease but would not permanently alter the genetic pool of the human race. The other form of genetic engineering would be the replacement of genes in such a way that parents would now transmit new genes to their offspring. Both of these forms of genetic technology are still speculative potentials for the future, but recombinant DNA methods have brought those possibilities closer to development. In a relatively short time it may be possible to consider gene therapy solutions to specific diseases, but the permanent replacement of genes is probably in the far future. In either case, however, it is important to realize that recombinant DNA technology is not the same as genetic engineering. It is a reality and is a problem that we must worry about. You will often hear critics argue that recombinant DNA work should be stopped because of its implications for genetic engineering. That is a possible strategy of social control, but you must realize if recombinant DNA work were not allowed not only would genetic engineering be further in the future but also all of the benefits that can derive from modern biology will be slower in coming.

The other type of potential risk that may be a consequence of the use of recombinant DNA methods would be a risk deriving from the production of harmful organisms during the conduct of recombinant DNA experiments. When I first participated in a public call for deep consideration of possible risks, I had serious fears about what types of hazards could occur if recombinant DNA methods were used without appropriate caution. Since that time I have listened to evolutionists and to infectious disease experts as well as to a range of critics who have presented scenarios of what kinds of dangers could be brought about by recombinant DNA work. I am today much less concerned about the hazards than I was before I began to listen to the debates. I have heard, for instance, how rare it is for an organism to survive the rigors of the natural world. I have realized how unlikely it is that any gene added to an unfit microorganism might make that microorganism suddenly capable of monstrous doings. I have realized that for an organism to survive in the natural world its fitness must be constantly tested by battles with nature and that laboratory organisms are poorly suited to the natural world because they have not had to battle it. I have realized that single genes are not the determinants of disease but that a whole constellation of genes must be present for an organism to be considered dangerous. Only genes working together and selected together can make an organism into a serious determinant of disease. So I believe that the risks that are being discussed in the popular press are wildly overstated.

When we first drew attention to the potential hazards of recombinant DNA work, we could see three areas in which single genes might be dangerous. These included the acquisition by bacteria of resistance to clinically useful antibiotics, the insertion of toxin-producing genes into benign bacteria and the insertion into bacteria of genes that may be carried in cancer-producing viruses. I can now see that these were the appropriate areas of concern because there are situa-

tions in which single genes might be a danger. The NIH guidelines for research involving recombinant DNA molecules places these three types of experiments in either the category of banned experiments or of experiments to be done only under the highest containment conditions. The guidelines then grade as best they can other types of experiments associated with much lower likelihood of potential hazards. It is my belief that the biological and physical containment provided by the guidelines is sufficient to control hazards that have any vague likelihood of occurrence. Admittedly, no guidelines can give us 100 percent freedom from risk, but that is not a criterion we ask of any aspect of our lives.

CONCLUSION

The public debate over recombinant DNA techniques has brought out very deep fears about the direction of modern biology. It is extremely important when such fears surface that a broad-ranging discussion takes place, including both scientists and the public, to air their fears and analyze their foundations.

I believe that the public has been unduly alarmed by the dangers of recombinant DNA research and that this is liable to lead to a patchwork of regulations relating to such research in the various municipalities and States across the country. In this situation I believe it is necessary for the Federal Government to step in and provide a defensible series of regulations which can allow the work to go forward under uniform conditions throughout the Nation. It would be ridiculous, to me, to have more stringent regulations in one jurisdiction than in another, especially because the types of hazards about which one might worry cannot be restricted to political boundaries.

There is one final distinction I consider very important. There are critics of recombinant DNA research who are attempting to stifle progress in all of modern biology. They are fearful of the consequences of modern biology, a fear which is generally directed toward genetic engineering. To cut off a field of research because of fear of the possibilities inherent in knowledge would be a suicidal policy for a civilized country. While we should not blind ourselves to the dangers that can come from scientific advances, if we stifle research as a way of avoiding the dangers we will condemn ourselves to a life with both no new knowledge and no new capabilities.

It is critically important for the subcommittee and its parent committee to periodically assess the state of modern biology. Because it is a field that touches on the basic elements of life it is a field with enormous potentials for both benefit and hazard. I trust, however, that you will be judicious in dealing with potential hazards so as not to stifle the development of knowledge which is prerequisite to new method for dealing with disease.

I thank you.

Mr. THORNTON. I want to thank you very much, Dr. Baltimore, for your fine statement.

Mr. Brown.

Mr. BROWN. Dr. Baltimore, the statement which you made on the last page about cutting off a field of research because of fear of the possibilities inherent in knowledge immediately led me to think that this is one of the oldest problems facing the human race. It apparently

was a factor in the situation that arose when Adam and Eve decided to test the health-giving properties of the apple, and I suspect the problem will be with us for a very long time.

That leads me to a question with regard to the ability of stopping, or even seriously curtailing, this type of research in this country, in view of two situations. One, can we control it in other countries? And, two, can we control it in the laboratories of some dedicated or fanatic researcher, a Dr. Jekyll, who might want to proceed with this on his own, or is such control even feasible? Are there any regulatory steps that this Government can take, other than that of moral suasion, that would effectively eliminate this if we decided that we wanted to?

Dr. BALTIMORE. I certainly believe that there are. With the appropriate legislation I would imagine that you could stop any open activities, probably any industrial activities also, in the area of recombinant DNA research. I see no reason why not. The problem of fanatics is with us all the time.

Mr. BROWN. This is specifically the problem that we face in the nuclear field, where it's now becoming possible theoretically for a fanatic to construct a nuclear bomb. We have laws against it, but we couldn't stop it.

Dr. BALTIMORE. No. I don't believe anything can stop a fanatic, laws or anything else. It's not clear to me, however, that were I interested in any type of fanatic activity that I would go to recombinant DNA techniques as a way of developing a weapon. There are commonly available bacteria which are bad enough, and there are nuclear weapons which are bad enough.

I think you've probably heard the simplicity of these techniques somewhat overstated. It does take a certain amount of sophistication in microbiology, in enzymology, and genetics to handle these techniques.

It is certainly true that as a professor I could work with a group of students and get them to do such experiments, but were I working in isolation in my basement I think I would have a pretty difficult job constructing anything dangerous. So I don't actually believe that the terrorist scenario in relation to recombinant DNA is a terribly serious one, at least at the present. I think there are much worse problems along those same lines.

Mr. BROWN. When I use the term "fanatic" I mean somebody like Galileo, or some scientist who decided to be a heretic.

But you haven't addressed the "other country" problem. Can we stop or regulate the British or French or Russian recombinant DNA research?

Dr. BALTIMORE. We have certainly been the leading country in considering the hazards, largely because it was a committee of the National Academy of Sciences that originally drew attention to the problem, and so the ball has been in our court all along.

If we went as far as to ban the research entirely, I feel certain that at least some, if not many, countries would not go along with that, and so the research would continue on in the world. But again, it's certainly true that we could make a significant dent in the amount of recombinant DNA work being done in the world if that were deemed to be appropriate national policy.

Mr. BROWN. Wasn't it in a British lab that Crick and Watson did their research?

Dr. BALTIMORE. Yes, they worked in Great Britain.

Mr. BROWN. I have no further questions.

Mr. THORNTON. Thank you very much, Mr. Brown.

Dr. Nathans, would you like to comment on that?

Dr. NATHANS. May I make a response to part of that question, that has to do with how you enforce regulation?

I think it pinpoints the difficulty in enforcing any regulation of this sort 24 hours a day, no matter what the law says, and I think it's a very strong argument for the need to depend on local groups to take responsibility, for example, Institutional Biohazards Committee, and have an institution take responsibility for enforcing those regulations.

Mr. THORNTON. Dr. Cavalieri?

Dr. CAVALIERI. I would like to make two comments about Dr. Baltimore's statement.

The first concerns the cause of cancer in industrialized areas. I think the statistics are overwhelming that chemical carcinogens, pollutants, are related to this. Whether they are the direct cause of cancer or not, one doesn't know. But I don't think it's appropriate to cast if off so easily, despite the apparent expert opinion of Dr. Doll.

It reminds me a little bit of the rage that went on 20 years ago when people were trying to decide the effect of smoking on health and, of course, everybody remembers the arguments. But, as it turned out, the statistics were clear.

I'm not saying that all cancers are caused by chemicals and that eliminating them would be an ample solution of the problem. I'm saying that it would be a good place to start since we have a vast body of data, even if some people question it, and if I personally were directing research, that's where I would spend my money, rather than on recombinant DNA.

The second comment I wanted to make concerns the question of science versus technology. I don't think Dr. Baltimore made the distinction clear. He spoke of biology as a whole, and I agree with that. It has many parts, and that recombinant DNA is one of the vital parts of it, or could be a vital part of it. I think recombinant DNA is an interesting technique, and perhaps should be pursued after we decide whether we want to pursue it.

But, I am not against science. I am against science as a technology. That's very important because it impinges on the very important question: Are we trying to stifle the intellect? Well, we are not. We are trying to stifle the industrial application for profit motives of devices, of inventions, whatever you want to call them, the scientists are going to produce. This is not antiscience, and I don't think that that should be put in that light, and I don't know that Dr. Baltimore meant to say that, but it's not an antiscience movement.

Mr. THORNTON. Dr. Cavalieri, your comments has caused Dr. Cape's hand to come up. May I ask for his continued response, Mr. Brown, or have you completed your questions?

Mr. BROWN. I've finished.

Mr. THORNTON. OK. Dr. Cape.

Dr. CAPE. Thank you, Mr. Chairman.

Nor do I think, in fairness to the views of Dr. Signer, Dr. Cavalieri, and others, if it's not an antiscience position should it be an anti-industry position.

I'm new to this public debate, but I remember college debating. You state somebody else's case, you set up a straw man and then you knock it down. I could, but I'm not going to debate the straw man that the search for truth can't be challenged, or the straw man that proponents of this work believe it will solve some of the social problems, which clearly require other social approaches, or the straw man that U.S. industry is racing into this field—U.S. industry is not racing into this field. Many people think it's racing the other way. Profits are very far away, and most companies are shying away from it—and the straw man that we have no options for control other than to ban the work altogether. We've got the Food and Drug Administration, for example.

There is one straw man, sort of, that I would like, if I can have 2 or 3 minutes to reply to, which has to do with the testimony at NIH and at the Department of Commerce, and which we've heard a lot of hearsay about what went on there. But I was there, and I don't agree with what I hear.

Mr. THORNTON. Are you speaking with regard to the patent question? You did summarize that in your testimony.

Dr. CAPE. No; I'm speaking with regard to U.S. industry's, if it can be so described, position with respect to the guidelines, the allegation that's been made repeatedly that U.S. industry is shifting its position, that it met with authorities on several occasions to oppose the guidelines, and now somehow, for reasons that are perhaps all too clear, U.S. industry is now falling into line, so to speak.

As I say, I was present at those hearings, and that's very far from what went on.

Mr. THORNTON. Are you referring to Dr. Wald's distinction between research and production in the NIH guidelines?

Dr. CAPE. Partly. But I'm also referring to Dr. Wald's statement that back in June the representatives of industry met with Dr. Fredrickson to oppose the guidelines and they met with Dr. Ancker Johnson in November again to take essentially a hostile position, and, as I say, I have some remarks about that.

Mr. THORNTON. Is it your belief that the industry position has been consistent?

Dr. CAPE. Relatively consistent, with one significant shift, which I think is worth mentioning.

Mr. THORNTON. Please mention it.

Dr. CAPE. At NIH last June and again at the Department of Commerce last November every industrial representative was asked, and every one replied that the company that they represented applauded the initiative of the scientists who blew the whistle on themselves, the extensive work that went into the promulgation of the NIH guidelines, and each representative endorsed the guidelines and indicated that their firm would adhere to them—let me repeat: unanimous, applauded, endorsed, would adhere, and this goes back to last June. This is not my interpretation of a report I read, or what somebody told me. I was there.

Mr. Chairman, the same thing happened again at the Department of Commerce. We were invited to a dialog. We were asked for our views. We were asked to look ahead. We were asked to make suggestions.

It seems generally agreed on all sides that the guidelines are today's perceptions of prudence. They are not cast in stone, but they're to be changed.

So, yes, it was pointed out that ultimately commercial production will require reexamination of the 10-liter limit. That's the production-research distinction that Dr. Wald mentioned yesterday, and that until that is done there will probably not be any commercial production. And, yes, it was pointed out that business in today's society is structured competitively, and that most companies would be reluctant to make substantial investments in any field unless they felt that their proprietary interest could be somehow protected. I stress "somehow" because no one had any good ideas, and at that time this Catch-22 aspect of giving up any hope of patent protection by complying with the guidelines wasn't yet fully described.

But isn't that why we are having a dialog? Shouldn't we have more? We're in a position where we're damned if we do; we're damned if we don't. If listening to the dialog causes a change in the position, then the position is described by some people as "shifty." Well, perhaps it's shifting, but it's shifting in response to the dialog.

Mr. THORNTON. Of course, I think that's the purpose of gaining information about any subject, to assist in formulating a position on the basis of additional discoveries, of additional knowledge.

Mr. Ottinger.

Mr. OTTINGER. Thank you, Mr. Chairman.

With respect to the testimony of Dr. Cape, I just don't think that private industry is the proper repository for the protection of the health and safety of the American people. I just don't think that that's the function of our free enterprise system. We've seen time and time again where private industry, if there's a profit to be made, will do anything that's legal, and sometimes things that are illegal, including continuing to pour known poisonous viruses into the environment, such as Kepone, PCB's and EPS'. It's the proper function of government to protect the health and safety of the population, to set those guidelines.

So that I really feel very strongly that we have an obligation to act. To the extent that there is a real threat, it is our responsibility. To the extent that the companies are goodhearted and socially responsive, or whatever, that's nice. But I don't think we can rely on that.

Dr. CAPE. Absolutely. I agree with you, Mr. Ottinger, and I hope that you do take that initiative.

Mr. OTTINGER. But you say that we should be slow and considerate and that we don't have to worry about corporations producing this, these DNA recombinant products. It think if there's a profit in it they will. I don't know if there's a profit in it or not. Your estimation is that that's some time off.

I do think that we ought to act if there is a public health need.

Dr. Baltimore and Dr. Nathans, as I say, I'm just terribly concerned, because we who are not scientifically qualified, for the most part, have an assigned duty of protecting the public interest. Hearing from emi-

nent and well-qualified scientists in this field, testimony such as you have given, that the risks are minimal, potential benefits are considerable, and this is a field of knowledge that should be pursued; and hearing from equally well-qualified distinguished scientists that the benefits are very speculative, that the risks are very great. As legislators why should we not, being faced with that dilemma, err on the side of caution; why should we not say, "Let's stop and resolve these problems until we can get a firmer determination of the risks."

Mr. THORNTON. Dr. Baltimore.

Dr. BALTIMORE. Mr. Ottinger, I don't think your formulation is correct. I spent pages saying that the benefits are speculative. Now, I guess I'm an optimist in believing that there will be benefits.

I used the example of the electron microscope, but I could have used any other major discovery of the last few hundred years, which has brought us from the dark ages of medicine into our present situation where we have control over infectious diseases. We have yet to solve the problems of cellular diseases, and I really believe that there will be knowledge that will come that will help us solve the problems of cellular diseases, but that's speculative.

Mr. OTTINGER. The thing is, we have had a lot of very capable testimony, including testimony from Dr. Cavalieri and Dr. Signer here today, indicating that this is very dangerous stuff that we're dealing with and that there really ought to be a better evaluation of the risks before we proceed, certainly, to any kind of application. Perhaps in some areas, before we proceed with research, maybe there is an area of knowledge better left unknown. I would like to explore that a little bit with Dr. Cavalieri: How far would you go on a moratorium?

But the thing is, we are faced with a quandary which we can't resolve because we are not scientifically qualified, and the eminent scientists say—forget the benefits side—"The risks are great," and, "The risks are minimal." As legislators then isn't our responsibility to say, "Let's wait until the scientists get their act together. Let us err on the side of safety."

Dr. BALTIMORE. Scientists will never get their act together, so you'll be waiting forever. There are deep divisions, but I don't think the divisions are exactly along the line that you state because even the deepest opponents of recombinant DNA research consider the risks minimal, in the sense that they don't think that every experiment that's going to be done presents a hazard. They think that there will ultimately be an experiment done that presents a hazard, and that's minimal, but, in their view, not acceptable.

Mr. OTTINGER. But they're already recommending that research work with various kinds of these organisms be confined to fortresses, like Fort Detrick, that have been known to leak and that are by no means perfect in themselves; but, nevertheless, they are sending in there certain hazardous kinds of experiments that ought to be enshrouded by the strictest kind of containment.

Dr. BALTIMORE. That's what I was going to finsh up by saying, that the proponents are for continuing forward with this research under the NIH guidelines, which has somehow become a position that's treated as if it were irresponsible, whereas in fact I think it is, if anything, overly responsible. People in that position will completely agree that there are things that should not be done, that there are

things that should be done under very high containment, and so there really is no disagreement that there ought to be control, and there's no disagreement that the risks are minimal, and the arguments come up about what kinds of risks one is willing to assume, and how bad you think something could be, and so the risk then becomes a matter of great detail, and I must say that I have spent much more time than I wished over the last few years looking at the details of many, many scenarios, and I find them all very unlikely to ever eventuate.

I believe that Dr. Nathans has made a very similar kind of evaluation for himself. He and I sat in a room at MIT in 1974, and off the tops of our heads said, "You know, there may really be some serious problems here," and then have spent now years and years studying what those problems might be.

Mr. OTTINGER. We heard from one of your MIT colleagues and from the director of a lab in Cambridge who say that the laboratory procedures, the existing safeguards, are just frightening sloppy, that lab workers get all kinds of diseases from the materials with which they work, that even at the most protected institution that there was very serious exposure that occurred, and that, therefore, we have a right to be much more concerned, not only about DNA but about certain other kinds of biological research materials.

Dr. BALTIMORE. But that's not fair, because you said your job was to protect the public health and safety, not the safety of laboratory workers. The safety of laboratory workers is a much more limited problem. Now, it is only laboratory workers who have ever been infected by laboratories. They have never spread to the community, even from Fort Detrick, where in fact there were infections among laboratory workers. Not one of those infections ever spread to the community.

Dr. Cavalieri said it was the height of irresponsibility to put these laboratories into medical research institutions. Well, in medical research institutions they work with highly pathogenic organisms, the same doctors who go and see patients. They know how to wash their hands; they know how to put on laboratory coats; and they know from years and years of experience that that protects the patients. So that it is not a matter of——

Mr. OTTINGER. Patients are getting all kinds of biological diseases in hospitals. They're rampant in hospitals.

Dr. BALTIMORE. But those are not diseases that they're getting of the normal pathological sort. Those are diseases which are caused by being in the hospitals, not tuberculosis coming from the doctors, any more.

Mr. OTTINGER. I don't know that.

Dr. Cavalieri?

Dr. CAVALIERI. I would just make the simple comment that if something is happening, why add to it, why put a P3 or a P4 in a medical setting because diseases are known not to spread or for this or that reason. It's adding insult to injury. The argument is fallacious.

Mr. OTTINGER. I think your criticisms were valid. If I were to fashion, as I may do, legislation to provide a period of time for examination of DNA recombinant research and set up a commission, which I think ought to have at least a preponderance of public people on it, how far would you extend that moratorium? Would you extend the moratorium to all recombinant DNA research?

Dr. CAVALIERI. That cross the species barrier.

Mr. OTTINGER. Only the P4 category, as defined under the NIH guidelines at the present time, only commercial application?

Mr. THORNTON. I believe his response was only that DNA recombinant research which crosses the species barrier.

Dr. CAVALIERI. Yes.

Mr. THORNTON. And not the P1-type experiments?

Dr. CAVALIERI. Essentially, yes. That would mean a stopping of research until one wanted to decide to do it, after a great deal of public discussion. I'm not saying that it shouldn't be done eventually. Maybe that will be the will of the people. All I would plea for would be a little bit of sober discussion before, before we act.

Mr. THORNTON. Would the gentleman yield?

Mr. OTTINGER. Yes.

Mr. THORNTON. In that regard, I was concerned with your extraction from the body of your testimony of your suggestions for regulation to extend beyond the area of recombinant DNA research to other forms of genetic engineering, or manipulation.

This might result from selective breeding from other varieties of plants, or such techniques which have been pursued aggressively over many years in agriculture. I think it might be useful to express whether you really are concerned about developing regulations for this kind of experimentation or if you are limiting your remarks to the recombinant techniques.

Dr. CAVALIERI. I don't want to broaden them out to include—let me clarify my statement.

I modified my text as a result of Dr. Cape's comment. I'm not proposing a ban on all sorts of things. What I had in mind, when you asked me during my testimony, was looking seriously at all kinds of things, like new pesticides and things like that, which we are apparently supposed to be doing. So I wasn't thinking that all kinds of genetic engineering, such as conventional types, plant genetics, et cetera, would be cut out. No, I did not mean that.

Mr. THORNTON. I think it's useful to clarify that.

Dr. Nathans has been trying to get my attention. I promised Dr. Signer I would recognize him to respond to Mr. Ottinger's question.

Dr. SIGNER. Thank you.

I want, first, to applaud as heartily as I can Mr. Ottinger's suggestion that the thing to do is proceed conservatively when there's a difference of opinion. It's a rather bizarre feature of the controversy that the burden of proof seems to fall implicitly on the people who want to slow down or stop this research. It ought to fall on the people who want to go ahead; that is, until it's proven safe, if it is safe. But I don't think it is safe. I don't think the risk is minimal. I've never said that, and to characterize my position that way, as Dr. Baltimore did, was rather surprising, to say the least.

There are other surprising statements in Dr. Baltimore's talk. Dr. Baltimore said: "Our ability to prevent and to treat the diseases is limited by our knowledge of them." We've wiped out smallpox; we've wiped out cholera, and typhoid, and typhus. We don't know very much about how those diseases are caused, but what we do know is how to prevent them. We don't have to know the basis of diseases in order to prevent them. We have to learn how to prevent them, and that can be something very different.

Dr. Baltimore wants us to go on with recombinant DNA research because it's impossible to predict what useful knowledge will come from it. But if that's so, then you can't have it both ways. If it's impossible to predict where useful knowledge will come from, then we can look in some other direction with just as much chance of success.

What bothered me very much was the implication running through the whole of Dr. Baltimore's statement that recombinant DNA research is equivalent to modern biology, that recombinant DNA research is equivalent to basic research. So that to be against recombinant DNA research, he implied, is to be against modern biology, against basic research.

I certainly am not against basic research. I certainly am not against modern biology. Recombinant DNA is a tool; it's one way of getting somewhere. There are other ways to get there.

The last thing I want to comment on in Dr. Baltimore's testimony was the statement, "the permanent replacement of genes is probably in the far future." He implied that introducing into the human germ line genes that have been manipulated in the laboratory is extremely far away, that people can't inherit, manipulated genes.

It's not far away. It's very, very close. I refer to the experiments reported at the Roche Institute meeting on teratomas in May 1975 by Dr. Beatrice Mintz, where teratoma cells were introduced into embryos and were then passed on to the offspring of the adults formed from these embryos. Excuse the technical detail. The point is, we're very, very close to manipulating genes in the laboratory and then getting them back into an organism in such a way that they can be inherited. That's one of the things that those of us who are concerned about genetic engineering are worried about.

Mr. THORNTON. Thank you, Dr. Signer.

Dr. Nathans.

Dr. NATHANS. I can sympathize with the problems that Congressmen and Senators have in deciding what's the correct advice when the advice is conflicting. I would like to make a couple of points about that, however.

One. Some of the advisers are self-selected. They're people who volunteered advice and have been called on by legislators all over the country to give the same advice. I would submit that the Congress deserves expert advice on the problem at hand. This country has a number of very knowledgeable people in infectious diseases, in pathogenesis of infectious diseases, in epidemiology which it has not asked to testify on the questions at hand.

Second. I think the focus really is properly on risk. That there will be benefits, in terms of basic knowledge, is already established. What we cannot predict is where that knowledge will lead, in terms of practical application.

But I think it's not sufficient for a legislator, if I may, sir, to say that: "Since I get conflicting advice, I must take the worst prognosis." I don't think that solves the problem. I think one must try to analyze that advice and try to find out who can give the most cogent advice on the outstanding points, and I submit there are many people in the country who have not volunteered advice who could give such advice.

Mr. OTTINGER. I understand our time is up, and I want to thank the chairman for his very great indulgence.

We would welcome your suggestions of additional people to ask to appear either here or in the Health Subcommittee, I am sure, because we are struggling with what I consider a very difficult problem. I have grave apprehensions about shutting off inquiry into this whole field of knowledge where there may be beneficial results.

I think we have got to proceed with caution and the best advice we can get.

Mr. THORNTON. I would like to thank the gentleman for his remarks, and to ask each of the panelists if you would agree to respond to such additional questions in writing as may be submitted to you.

I want to thank you for your appearance today and for your very excellent testimony.

I do have some questions which I had wanted to ask. I don't have the time to do it. But I would like to leave the question open, and for your submission in writing, as to whether the danger of acquiring too much knowledge is the greater danger, or whether the danger of not seeking additional knowledge is the greater danger.

I think this panel has generally agreed that the pursuit of knowledge in basic science should not be impeded. I hope that's the conclusion from what has been expressed, and that what is sought here is a means of exercising some restraint over an assessment of risks and benefits, which is what this panel has been about.

Tomorrow at 9:30 we will meet in this room again to study the actions which the Federal Government and the governments of other nations have taken with regard to this research.

Thanking the members of the panel again, I now declare this hearing adjourned. Thank you.

[Whereupon, at 11:07 a.m., the subcommittee adjourned, to reconvene at 9:30 a.m., on Thursday, March 31, 1977.]

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

THURSDAY, MARCH 31, 1977

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY,
Washington, D.C.

The subcommittee met, pursuant to adjournment, at 9:30 a.m., in room 2318, Rayburn House Office Building, the Honorable Ray Thornton, the chairman of the subcommittee, presiding.

Chairman THORNTON. The subcommittee will come to order. This morning we continue the Subcommittee on Science, Research, and Technology's hearings on the science policy implications of the DNA recombinant molecule research issue.

This morning we are very pleased to have a distinguished panel of witnesses to assist us in our examination of actions taken by the Federal Government and the governments of other countries regarding DNA recombinant molecule research.

Dr. Donald Fredrickson, who is the Director of the National Institutes of Health, Bethesda, Md., is here as our first witness this morning.

Dr. Fredrickson, you have with you I believe some additional staff personnel. Would you like to introduce them?

Dr. FREDRICKSON. Thank you, Mr. Chairman. I would be very glad to do that.

To my far left is Dr. Bernard Talbot, who is Special Assistant for Intramural Affairs at NIH. Next to him is Dr. William Gartland, who is the Director of the Office of Recombinant DNA Activities at NIH. And on my right is Mr. Joseph Hernandez, who is from the Division of Legislative Analysis. And to my far right, at the far end of the table, we are very pleased to be joined by Dr. William J. Whelan, who is chairman of the department of biochemistry at the University of Miami School of Medicine.

Chairman THORNTON. We also extend our welcome to you, Dr. Whelan, and I appreciate very much your being with us this morning.

I understand that you have some time problems, Dr. Fredrickson, with regard to your own testsimony, and, accordingly, I would like to ask you to go first. We might have some questions to address to you, then, in order to allow you to leave if you do have a time problem, and ask that Drs. Talbot, Gartland, and Mr. Hernandez might remain aboard if possible if there are additional questions to be addressed to them.

Is that acceptable?

Dr. FREDRICKSON. Thank you very much, Mr. Thornton, and I will be very glad to leave my comrades here and to—to help you—and I will stay just as long as I can.

Chairman THORNTON. Very fine.

[A biographical sketch of Dr. Fredrickson follows:]

BIOGRAPHY

Dr. Donald S. Fredrickson

Dr. Fredrickson was born on the 8th of August 1924, in Canon City, Colorado, U.S.A. He completed his medical studies at the University of Michigan, and did his post-graduate work at the Peter Bent Brigham and Massachusetts General hospitals associated with Harvard University in Boston. From there, he moved as a Clinical Associate to the National Institutes of Health in 1953, where he has carried out the major part of his clinical and laboratory investigations.

His earliest interests centered on the mechanisms of synthesis, transport, and the metabolism of fats and lipoproteins, studies which included the effect of different drugs in reducing cholesterol and other fats in the blood. He published many experimental papers during the period 1955 to 1961, while a member of the Laboratory of Physiology and Cellular Metabolism of the National Heart Institute. In 1961, he was named Clinical Director of the National Heart Institute, and in 1966 he served for nearly two years as the Director of that Institute.

In 1968, he became the Director of Research of the then National Heart and Lung Institute and at the same time was Head of his own Laboratory of Molecular Diseases. His group carried out important work dealing with the structure of the lipoproteins, their importance in the transport of fats, and the genetic factors which regulated the metabolism and concentration of these lipoproteins in blood. During this time, he discovered the deficiency disease, Tangier Disease, and established the form of hereditary transmission of this lipoprotein deficiency state. A little later, he also discovered cholesterol ester storage disease, a second genetic disorder of fat metabolism.

During the period from 1965 to 1967, there occurred perhaps the most important and best known of Dr. Fredrickson's work, which is well-known throughout the scientific world: a system for classification of the hyperlipoproteinemias, which was rapidly accepted by the World Health Organization and shortly extended to all the textbooks and reports on this subject. This extended to clinicians the recognition of the degree of heterogeneity underlying different clinical states associated with hyperlipidemia and made more rational the understanding of the therapeutic action of diets and drugs in treating this problem.

BIOGRAPHY - Dr. Donald S. Fredrickson

In the last five years, Dr. Fredrickson's laboratory has appreciably contributed to knowledge concerning the apolipoproteins (the protein portion of the particles in which all fats circulate in plasma) including the description of several new apoproteins heretofore unknown, and completion of the amino acid sequence of various apoproteins and other data concerning their function and structure.

Dr. Fredrickson has received recognition for all his fundamental work, including the Gold Medal of the American College of Cardiology, the McCollum Award of the American Society for Clinical Nutrition, the James F. Mitchell Prize, and in 1973 was made a member of the National Academy of Sciences. In July of 1974, he became the President of the Institute of Medicine of this Academy.

STATEMENT OF DR. DONALD FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA

Dr. FREDRICKSON. I appreciate the opportunity to go first.

Chairman THORNTON. Yes, sir. We do have your prepared statement before us, and without objection that statement will be made a part of the record, and I'd like to now invite you to proceed as you may choose.

[The prepared statement of Dr. Donald Fredrickson is as follows:]

FOR RELEASE UPON DELIVERY

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON RECOMBINANT DNA RESEARCH

BEFORE THE

SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY

OF THE

HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

MARCH 31, 1977

93-481 O - 77 - 13

I. INTRODUCTION

Good day, Mr. Chairman and other Committee members. I am pleased to appear before you today to discuss Federal policies concerning recombinant DNA techniques. Specifically, I want to tell you about the activities of two organizations--the National Institutes of Health and the Federal Interagency Committee on Recombinant DNA Research.

Recent scientific developments in genetics, particularly in the last four years, have culminated in the development of a powerful new tool for research--the ability to join together genetic materials from different sources in cell-free systems to form recombinant DNA molecules. I would like to emphasize the point that recombinant DNA is a tool for accomplishing the types of research that scientists have been pursuing for decades. "DNA"--which is the shorthand way of saying "deoxyribonucleic acid"--is the material that determines hereditary characteristics of all known cells. Thus altered cells are created with the ability to replicate themselves. From testimony already received, you are aware that this new and powerful tool of science has generated great hope and excitement and, concomitantly, many expressions of concern.

Research using recombinant DNA techniques offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly (in the future) to create microorganisms useful in producing medically important substances for the treatment and control of disease. Aside from

potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the large-scale production of enzymes for industrial use; and potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There may be risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA microorganism may alter the host in unpredictable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment.

Until the potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions ensuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations. That is, the desire to allow this significant research to continue while protecting humans and the environment from the effects of potential hazards whose nature and the occurrence of which is as yet uncertain. I would like to review with the Committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my testimony to the work of the Interagency Committee.

II. DEVELOPMENT OF THE NIH GUIDELINES

The first step in the development of the Guidelines was taken by the scientific community. Scientists engaged in research using recombinant DNA technology first expressed concern about the potential biohazards at the Gordon Research Conference on Nucleic Acids in July 1973. At their request, the National Academy of Sciences created a committee that called for a moratorium on certain types of experiments and for an international conference to consider this problem further. The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research. At the International Conference on Recombinant DNA Molecules held at Asilomar, California, in February 1975, temporary guidelines were issued, including a continued moratorium on some experiments but allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

The NIH Recombinant DNA Molecule Program Advisory Committee was established in October 1974 to advise the Director of NIH. In December 1975, the Committee, after several open meetings, recommended proposed guidelines for my review and decision.

To assist me in the review of the proposed guidelines, a special meeting of the NIH Advisory Committee was convened in February 1976. Members of the Committee represented not only science but such other disciplines as law, ethics, and consumer affairs. Comments received from committee members and a number of public witnesses represented a

wide range of views. Follow-up written comments were also solicited. In April, the NIH Recombinant Advisory Committee considered these comments from the February meeting, and a number of changes to the guidelines were made. Concurrently, meetings for information exchange were held with representatives from other Federal agencies and private industry as well as with Congressional staffs. Finally, on June 23, 1976, with the approval of the Secretary of HEW and the Assistant Secretary of Health, the NIH issued guidelines to govern the research it supports involving recombinant DNA molecules. The NIH Guidelines established strict conditions for the conduct of this research, prohibiting certain types of experiments and requiring special safety conditions for other types. The provisions were designed to afford protection--with a wide margin of safety--to workers and the environment. Two weeks later, on July 7, 1976, the NIH Guidelines--together with a document indicating the basis of my decisions on principal issues--were published in the Federal Register for public comment.

Over 40,000 copies of the Guidelines have been widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and major professional research societies.

III. NIH ACTIVITIES FOLLOWING RELEASE OF THE GUIDELINES

Subsequent to the release of the Guidelines, NIH initiated several actions.

A. Office of Recombinant DNA Activities

To facilitate implementation of the Guidelines, the NIH, in June 1976, established the Office of Recombinant DNA Activities: to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees; and to monitor reports and information concerning accidents, containment, and safety research innovation.

B. Published Proceedings

In August 1976, the NIH published a volume containing the transcript of the February NIH public hearing on the proposed guidelines, voluminous related correspondence, and the results of relevant meetings held prior to the release of the Guidelines in June. A second volume is planned for publication in late Spring documenting the correspondence that the NIH received on the Guidelines, the Environmental Impact Statement, and the Departmental patent policy.

C. Environmental Impact Statement

The NIH, in accordance with the National Environmental Policy Act of 1969, undertook an environmental impact assessment to review environmental effects, if any, of research that may be conducted under the Guidelines. The NIH Guidelines were released prior to the completion

of the assessment because they provide greater protection for the public and the environment than the Asilomar Guidelines or no guidelines.

A Draft Environmental Impact Statement was filed and published in the Federal Register on September 9, 1976, to afford additional public review and comment. The draft statement has been analyzed and comments received are addressed in the final Environmental Impact Statement to be published soon.

D. Department Patent Policy

In June, shortly before the release of the Guidelines, Stanford University and the University of California asked NIH to review DHEW policies relating to the patenting of inventions perfected through the use of recombinant DNA techniques and financed by NIH. Under current DHEW patent regulations, invention rights to discoveries developed under the Department's research support are normally allocated in either of two ways:

- The Department may enter into an Institutional Patent Agreement (IPA) with a university or other nonprofit institution that has adequate mechanisms for administering patents on inventions. The IPA provides the institution the first option to own all inventions made in performance of Department grants or contracts, subject to a number of conditions deemed necessary to protect the public interest.
- For those institutions that have not entered into a patent agreement with the Department, determination of ownership is deferred until an invention has been made, at which time an institution may petition the Department for ownership of the invention.

The NIH solicited opinions from a number of different groups in the scientific community and the public and private sectors concerning departmental patent policies, with respect to recombinant DNA research inventions. An analysis of the issues raised by the commentators is currently under review.

IV. THE INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH

I would now like to devote the remainder of my testimony to the activities of the Interagency Committee on Recombinant DNA Research. This Committee was created, with the approval of President Ford, to address extension of the NIH Guidelines beyond the NIH, to the public and private sectors.

The specific mandate of the Interagency Committee is as follows: to review the nature and scope of all recombinant DNA research conducted in the United States, to determine the applicability of NIH standards to regulate this research nationally, to recommend mechanisms to ensure that the standards are being complied with, and to facilitate exchange of information throughout the Federal sector. The Committee is advisory to the Secretary of Health, Education, and Welfare. It includes representatives of Federal Departments and Agencies that support and conduct recombinant DNA research (or may do so in the future), and representatives of Federal Departments and Agencies that have present or potential regulatory authority in this area. At the Secretary's request, I serve as Chairman of the Committee.

Two meetings of the Committee were held in November 1976. The first of these, on November 4, was devoted to a review of the development of the NIH Guidelines. The Committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including Canada, the United Kingdom, the Scandinavian countries, most other parts of western Europe, eastern Europe, the Soviet Union, and Japan.

In many countries, appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries have acted to establish guidelines to govern the conduct of this research, including the United Kingdom and Canada. In the United Kingdom, a parliamentary committee addressed the issue and indicated that work in this area should continue under appropriate safety conditions. Scientific advisory committees of international organizations, such as the World Health Organization, the International Council of Scientific Unions, and the European Molecular Biology Organization, have made similar recommendations.

The European Science Foundation, representing member nations from Western Europe and Scandinavia, has recommended to its members that they follow the guidelines of the United Kingdom. These guidelines are, in intent and substance, very similar to those of the National Institutes of Health. The NIH is currently working very closely with the United Kingdom and the European Science Foundation to ensure a commonality of

standards in carrying out this research. Thus far, there has been very close cooperation and coordination among the various international and national scientific bodies, with a view to reaching a consensus on safety practices, programs, and procedures.

At the meeting of the Committee held on November 23, 1976, the Federal research agencies discussed their activities and possible roles in the implementation of the NIH Guidelines. All research agencies endorsed the Guidelines to govern recombinant DNA research. At present, the NIH, the National Science Foundation, the Veterans Administration, and the U.S. Department of Agriculture are supporting or conducting such research. The Department of Defense, National Aeronautics and Space Administration, and the Energy Research and Development Administration do not at present conduct such research, but all have endorsed the NIH Guidelines to govern future research should it be undertaken.

A. Subcommittee Review of Existing Legislation

Also at the November 23 meeting, the Federal regulatory agencies reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of research involving recombinant DNA technology. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel.

The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in

the United States (whether or not federally funded) and would include at least the following regulatory requirements:

(1) Review of such research by an institutional biohazards committee before it is undertaken.

(2) Compliance with physical and biological containment standards and prohibitions in the NIH Guidelines.

(3) Registration of such research with a national registry at the time this research is undertaken (subject to appropriate safeguards to protect proprietary interests).

(4) Enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much laboratory research involving recombinant DNA techniques, but that no single legal authority or combination of authorities currently existed that would clearly reach all research and other uses of recombinant DNA techniques and meet all stated requirements. Although there is existing authority that might be interpreted broadly to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed to warrant detailed consideration:

(a) The Occupational Safety and Health Act of 1970 (Public Law 91-596)

(b) The Toxic Substances Control Act (Public Law 94-469)

(c) The Hazardous Materials Transportation Act (Public Law 93-633)

(d) Section 361 of the Public Health Service Act (42 U.S.C. 264).

In addition, several other laws were examined. The Clean Air Act, the Federal Water Pollution Control Act, the Resources Conservation and Recovery Act, and the authorities of the FDA and the Department of Agriculture.

The full Committee adopted the report of its Subcommittee and agreed that new legislation was required.

B. Interagency Committee Analysis of Elements for Legislation

In considering the elements for legislation, the Committee reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research.

Among Congressional proposal reviewed were S. 621, "The DNA Research Act of 1977," introduced by Senator Dale Bumpers, and the companion measure introduced by Representative Richard L. Ottinger in the House (H.R. 3591). The Committee also noted the resolution introduced by Representative Ottinger on January 19, 1977 (H. Res. 131), requesting DHEW to regulate recombinant DNA research under Section 361 of the PHS Act.

Among State and local activities reviewed were recommendations by the New York State Attorney General's Environmental Health Bureau for State regulation, and the Cambridge (Massachusetts) City Council's resolution on recombinant DNA research.

Several committee representatives also reported on meetings with other interested parties whose views had been solicited on legislation to regulate recombinant DNA research. Those who were contacted include agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry. At my request, the Industrial Research Institute and the Pharmaceutical Manufacturers Association are surveying their member firms to determine the scope of the research efforts in the private sector. The Pharmaceutical Manufacturers Association has endorsed the NIH Guidelines as standards for conduct of this research.

In considering elements of proposed legislation, a number of issues were raised and discussed fully by the Committee. After detailed deliberations at meetings on March 10 and 14, 1977, the Committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by the Committee were presented in an Interim Report transmitted to HEW Secretary Califano on March 15, 1977. Secretary Califano, in releasing the report on March 16, stated that "legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time." He went on to say, "...I believe such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area. We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the

risks and benefits posed by use of recombinant DNA techniques without Government regulation."

The Department is now drafting legislation in the light of the recommendations made by the Committee. This legislation should be ready soon.

Mr. Chairman, I would like to submit for the record the Federal Interagency Committee's "Interim Report on Suggested Elements for Legislation," along with a copy of the Secretary's press release.

With your permission, I would like to review briefly some of the major elements addressed by the Committee. The Committee determined that the Department of Health, Education, and Welfare is the appropriate locus in the Government for the regulation of the use and production of recombinant DNA molecules. In reaching this determination, the Committee took into account existing roles of certain agencies within DHEW--for example, that of the NIH in developing the Guidelines, and of the Center for Disease Control and Bureau of Biologics (FDA) in regulating infectious agents and biological products. The Committee also had before it the petition by the Environmental Defense Fund, requesting DHEW to issue regulations for recombinant DNA research.

The Committee reviewed at great length the nature and scope of regulation. Consideration was given to regulation of all laboratory research where hazardous or potentially hazardous substances were employed. There was general Committee agreement that present legislation should be restricted to recombinant DNA techniques.

However, I have established a committee at the NIH, chaired by Dr. Richard Krause, Director, NIAID, to study and recommend, if necessary, safety standards for other NIH-supported research involving actual or potential biohazards. The preliminary report is expected shortly, and I will keep the Committee informed of the progress on this NIH review.

Regulation of just the research aspects of recombinant DNA techniques presents a problem because of the difficulty in determining the border between research and pilot production. Therefore, the Committee recommends that regulation cover the production or use of recombinant DNA molecules. Such language would include research activity, and makes immaterial possible concerns whether a given activity constitutes research, pilot production, or manufacture. The Committee recommends that the Secretary, in specific instances, in consultation with appropriate regulatory agencies, be allowed to determine the nature of the activity and should defer to a regulatory body that the Secretary determines is better empowered and equipped to deal with it.

There was general agreement by the Committee that registration of projects involving the use or production of recombinant DNA molecules was necessary. The Committee also recommends that facilities be licensed and that the terms of the license include acceptance of responsibility for the particular activities and individuals at the facility. The Committee concluded that licensure of the facility and registration of projects would be more feasible and would more adequately meet the needs

for safety monitoring rather than licensure or registration of individuals engaged in research.

The Committee urges full disclosure to the appropriate regulatory body of all relevant safety and scientific information pertaining to the use or production of recombinant DNA molecules. However, the Committee recognizes the important world-wide commercial potential of recombinant DNA molecules in medicine, agriculture, and other areas of science and technology. It believes that the potential commercial uses of recombinant DNA techniques require that information of a proprietary nature and patent rights be given appropriate protection from disclosure by the regulatory agency receiving such information. However, the Secretary may immediately release information if public safety requires it.

Because the potential hazards posed by the use of recombinant DNA techniques extend beyond the local to the national and international levels, the Committee recommends that a single set of national standards must govern and that, accordingly, local law should be preempted to ensure national standards and regulations. The Committee, however, took into account the activities at the State and local levels on regulation of recombinant DNA research. It was agreed that, if a State passes a law imposing requirements identical to those contained in the Federal legislation, then the Secretary may enter into an agreement with the State to utilize its resources to assist the Secretary in carrying out his duties.

Protection of workers was also considered by the Committee. Training of workers in proper laboratory techniques and long-term medical monitoring are important aspects of worker safety and were endorsed by the group.

A number of other recommendations are made, and I can discuss them further if you have questions. I would like to emphasize that the work of the Interagency Committee has been done in a most cooperative and helpful way.

DHEW will continue to cooperate and coordinate with relevant Federal Departments and Agencies in this important matter.

IV. CONCLUSION

In conclusion, this much is clear: the international and national scientific community is in substantial agreement that, until the potential hazards of recombinant DNA techniques are better understood, a common set of standards must everywhere exist for the use of those techniques. The question being debated now is how this is to be accomplished. The substance of all guidelines is sufficiently similar; how to apply them locally and nationally remains the issue.

In the United States, this question has attracted far more public attention than in other countries. A number of local jurisdictions or states are engaged in action or debate.

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Finally, I want to note that biomedical research is entering a new era in its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives under concerned public scrutiny. NIH has responded to these concerns by requiring the formation of review boards to oversee human experimentation, animal care, and now DNA recombinant experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need not--and, indeed, should not--go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights--call it inspiration, if you like--of individual scientists.

Dr. FREDRICKSON. I should like to summarize briefly some of the elements in that larger statement which has been submitted for the record.

Mr. Chairman, I am pleased today to be able to appear before you to discuss Federal policies concerning recombinant DNA techniques.

Specifically, I should like to tell you about the activities of two organizations—the National Institutes of Health and the Federal Interagency Committee on Recombinant DNA Research.

Recent scientific developments in genetics, particularly in the last 4 years, have culminated in the development of a powerful new tool for research—that is the ability to join together genetic materials from different sources in cell-free systems to form what are called recombinant DNA molecules. I would like to emphasize the point that recombinant DNA is a tool for accomplishing certain types of research that scientists have been pursuing for decades.

From the testimony already received, you are aware that this new technology has generated great hope and excitement and, concomitantly, many expressions of concern.

Research using recombinant DNA techniques offers great promise. But there may be risks as well. Until these potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions insuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations, that is, the desire to allow this significant research to continue while protecting humans and the environment from the effects of potential hazards whose nature and occurrence is as yet uncertain.

I would like to review briefly with the committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my statement to the work of the Interagency Committee.

The first step in the development of the guidelines was taken by the scientific community. Scientists who were engaged in research using recombinant DNA technology first expressed concern about the potential biohazards at a Gordon Research Conference on Nucleic Acids which was held in July 1973.

At the request of the attendees at that meeting, the National Academy of Sciences created a committee that called for a moratorium on certain types of experiments and for an international conference to consider the problem further.

The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research.

At the International Conference on Recombinant DNA Molecules held at Asilomar, Calif., in February 1975, temporary guidelines were issued including a continued moratorium on some experiments while allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

The NIH Recombinant DNA Molecule Program Advisory Committee—Recombinant Advisory Committee—was established October 1974 to advise the Director of NIH. In December 1975, the committee, after several open meetings, recommended proposed guidelines for my review and decision.

To assist me in the review of the proposed guidelines, a special meeting of the advisory committee to the Director, NIH, was convened on February 1976. Members of this committee—which is to be distinguished from the Recombinant Advisory Committee—represented not only science but such other disciplines as law, ethics, and consumer affairs.

Comments received from committee members and public witnesses represented a wide range of views. Follow-up written comments were also solicited from several diverse viewpoints, including the Environmental Defense Fund.

In April, the NIH Recombinant Advisory Committee considered these comments developed from the February session and comments made thereafter, and a number of changes to the guidelines were made. Concurrently, meetings for information exchange were held with representatives from other Federal agencies and private industry, as well as with congressional staffs.

Finally, on June 23, 1976, with the approval of the Secretary of HEW and the Assistant Secretary of Health, the NIH issued guidelines to govern the research it supports involving recombinant DNA molecules. The NIH guidelines established strict conditions for the conduct of this research. The guidelines prohibit certain types of experiments and require special safety conditions for other types. The provisions are designed to afford a wide margin of safety to workers and the environment.

Two weeks later, on July 7, 1976, the NIH guidelines—together with a document indicating the basis of my decisions on the principal issues—were published in the Federal Register for public comment.

Over 40,000 copies of the guidelines have been widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and major professional research societies.

Subsequent to the release of the guidelines, NIH undertook several actions. To facilitate implementation of the guidelines, the NIH, in June 1976, established the Office of Recombinant DNA Activities to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees which are required by the guidelines; and to monitor reports and information concerning accidents, containment, and safety research innovation.

I would like to devote the remainder of my statement to the activities of the Interagency Committee on Recombinant DNA Research. This committee was created, with the approval of President Ford, to address extension of the NIH guidelines beyond the NIH, to the public and private sectors.

The first meeting of the committee, on November 4, 1976, was devoted to a review of the development of the NIH guidelines. The committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including most parts of Western Europe, Eastern Europe, the Soviet Union, and Japan.

In many countries, appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries, including the United Kingdom and Canada, have acted to establish their own guidelines to govern the conduct of this research.

If I might digress a moment I would like to expound a bit further, Mr. Chairman, on the activities abroad, because they bear importantly on activities at home.

We have at NIH, through other agencies in our Government and through many scientific societies, been in close contact with many of the scientists and many of the officials abroad who engage in activities, either research or administrative, that relate to the use of these techniques.

Last fall I was privileged to visit a number of molecular biology laboratories in Europe. I stopped in Britain to discuss the Williams report, which is the basis for the United Kingdom guidelines. I talked to members of the European Science Foundation, which is the organization within the European Economic Community that has taken the lead in attempting to have a uniform type of procedure governing the use of these techniques throughout Europe.

We also have been in contact with the genetic manipulation advisory groups of a number of countries. These GMAGs are the operating units that were established under the United Kingdom guidelines adopted by the European Science Foundation as a structure for organizing control of these activities throughout the EEC. We have been in contact with these GMAG's from a number of countries and, most particularly, we had very close contact with Sir Gordon Wolstenholme, who is the chairman of the United Kingdom GMAG.

Chairman THORNTON. Is the formulation of policy in the European countries a matter of public debate, or is this work being done primarily through the institutions of Government and scientific organizations?

Dr. FREDRICKSON. The work has been carried out almost entirely by a group of advisory committees, some of them quasi-governmental, some of them actually private but reporting to governments. There has been very little public debate or press comment, about recombinant DNA activities in Europe, nothing comparable to that which has occurred in the United States.

There has been one question raised in the Swiss Parliament, for example, in the last 3 years, which was quickly answered by the Government.

There have been, on the other hand, almost none of the activities that have attended the development of guidelines in this country. Perhaps it's just a different manner of approaching these problems in the rest of the world.

But I would say that the activities within the scientific community have been very uniform. That is complete agreement across the world of molecular biologists and others who are using these techniques, that its extremely important to have a uniform set of standards throughout the world.

Chairman THORNTON. Are you suggesting that the assessment of risks of which experiments may be more dangerous and require increasing levels of containment or might be prohibited altogether, that these standards are rather uniformly accepted by the scientific community and the several nations which are conducting the research?

Dr. FREDRICKSON. Yes I am, Mr. Chairman. The United States or NIH guidelines, the United Kingdom guidelines, and the Canadian guidelines, in general, as they deal with recombinant DNA research, are all children of Asilomar. That is, they have been based on the ac-

ceptance of a generally uniform method of prescribing containment for experiments according to the same design as you see in the NIH guidelines.

Chairman THORNTON. Thank you, Dr. Fredrickson.

Please continue with your statement.

Dr. FREDRICKSON. In fact, this agreement among scientists now leaves us at the second stage of development in this problem, and that is how to extend these guidelines throughout the world, how to compel compliance with them.

We find all nations dealing individually with this problem because a single country offers the largest political unit in which law can be applied effectively in dealing with these problems.

With the effective development of statutes or application of available and existing regulations, it should be possible to blanket the whole world with a quite uniform set of standards of conduct for the use of these techniques.

We have also been in indirect contact, through the International Council of Scientific Unions, with scientists, and molecular biologists in the Eastern European countries, including Professor Bayev, who is head of the Soviet Academy of Science Committee which is seeking to develop guidelines for use in the Soviet Union. Throughout all of these countries, the NIH guidelines and United Kingdom guidelines are being used, together or alternately, and thus there is really a quite uniform standard of conduct at the present time.

In addition to reviewing the activities abroad, the Interagency Committee at its November 4 meeting also had the Federal research agencies discuss their activities and possible role in the implementation of common guidelines. All of the research agencies endorsed the guidelines.

At the meeting on November 23, 1976, of the Interagency Committee, the Federal regulatory agencies reported on their regulatory functions, as they might relate to the use of recombinant DNA techniques. Following that review, a special subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of research involving recombinant DNA technology. All regulatory agencies were represented on this subcommittee, and assisted by attorneys from their offices of general counsel.

It was the conclusion of the subcommittee that no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques.

The full committee reviewed the findings of the subcommittee and adopted its report, and agreed that new legislation is needed.

The committee then turned to considering the elements for possible new legislation, and in doing so, it reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research.

Additionally, the views of several interested parties were solicited on legislation to regulate recombinant DNA research. Those parties included agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry.

After detailed deliberations at meetings on March 10 and 14, 1977, the committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by

the committee were presented in an interim report which was transmitted to HEW Secretary Califano on March 15, 1977.

The department is now drafting legislation in the light of the recommednations made by the committee, and the OMB is reviewing comments on such draft legislation. This legislation should be ready soon.

Mr. Chairman, I would like to submit for the record the Federal Interagency Committee's "Interim Report on Suggested Elements for Legislation," along with a copy of the Secretary's press release, which accompanied it.

Chairman THORNTON. Without objection, the material submitted will be made a part of the record.

[The material referred to follows]:

HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOR RELEASE AT 1:00 P.M. EST
Wednesday, March 16, 1977

National Institutes of Health
Storm Whaley (301) 496-4461

New legislation is necessary to regulate the use and production of recombinant DNA molecules, according to a report transmitted today to the Secretary of Health, Education, and Welfare.

In accepting the report from the Federal Interagency Committee on Recombinant DNA Research, Secretary Joseph A. Califano, Jr., said that the Department will immediately begin drafting legislation in the light of the recommendations made by the Committee.

Califano noted that he had been closely monitoring the recombinant DNA issue since his confirmation and that he had been in continuous communication with Dr. Donald S. Fredrickson, M.D., Director, National Institutes of Health and Chairman of the Interagency Committee.

"I recognize that legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time," Califano stated.

"But I believe that such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area.

(more)

"We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the risks and benefits posed by use of recombinant DNA techniques without government regulation," Califano said.

While agreeing with what he called the prudent recommendations of the Interagency Committee in this limited and most exceptional area, Califano reaffirmed his commitment to the principle of unfettered inquiry that applies in scientific research.

The Interagency Committee is composed of representatives of Federal departments and agencies that support and conduct recombinant DNA research or that have present or potential regulatory authority in this area.

The Interagency Committee recommended that any legislation should, among other things:

- place primary responsibility for the administration of the act on the Secretary of HEW;
- require any person engaging in such research, production, or use of DNA recombinant molecules to do so only at a facility licensed by the Secretary;
- require any person engaging in such activity to do so only after the project has been registered with the Secretary; and
- the Secretary should have authority to inspect facilities, make environmental measurements, and take other steps to ensure safety.

The Committee pointed out that this legislation would establish uniform standards for such activities throughout the Nation.

In addition, the Committee recommended that the NIH Guidelines for Research Involving Recombinant DNA Molecules become the national standard, with such modifications as the Secretary may consider necessary.

Califano stated that he asked HEW's General Counsel-Designate to work with Dr. Fredrickson, and the technical experts on the Interagency Committee, and to consult closely with the relevant Congressional committees in drafting legislation for clearance with the Office of Management and Budget and eventual submission to Congress, that would follow the Interagency Committee's recommendations.

CONTENTS

INTERIM REPORT OF THE
FEDERAL INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH:
SUGGESTED ELEMENTS FOR LEGISLATION
March 15, 1977

I. Introduction

Recent scientific developments in genetics, particularly in the last four years, have culminated in the ability to join together genetic material from different sources in cell-free systems to form recombinant deoxyribonucleic acid (DNA) molecules. DNA is the material that determines hereditary characteristics of all known cells. Recombinant DNA research offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly in the future, to create microorganisms useful in producing medically important compounds for the treatment and control of disease. Aside from the potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the large-scale production of enzymes for industrial use. Potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There are risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA in a microorganism may alter it in unpredictable and undesirable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment.

Or the altered bacteria might have a competitive advantage, enhancing their survival in some niche within the ecosystem.

Until the potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions ensuring safety. This was the fundamental principle that guided the Federal Interagency Committee on Recombinant DNA Research in its deliberations--that is, the desire to allow this significant research to continue while simultaneously protecting, as much as humanly possible, man and the environment from effects of potential hazards whose nature is as yet unknown.

The Committee formally adopted this interim report by unanimous consent, save for abstentions by the representatives from the Council on Environmental Quality and the Department of Justice.

II. Development of the NIH Guidelines on Recombinant DNA Research

Approximately three years ago, because of the perceived potential hazards, scientists engaged in this research voluntarily called for a moratorium on certain experiments pending an assessment of risk and the development of appropriate guidelines. These scientists called upon the National Institutes of Health (NIH), of the Department of Health, Education, and Welfare, to create an advisory committee to develop such guidelines. After what NIH considered to be extensive scientific and public review, it released guidelines on June 23, 1976, which established strict conditions for the conduct of NIH-supported research in this area. The NIH Guidelines prohibit certain types of experiments and require special safety conditions for other types. The provisions

are designed to afford protection with a wide margin of safety to workers and the environment. The NIH Guidelines were published in the Federal Register on July 7, 1976, for public comment.

The NIH also prepared and filed in the Federal Register on September 9, 1976, a Draft Environmental Impact Statement on the Guidelines for public comment. The final NIH Environmental Impact Statement will be published shortly. In August 1976 the NIH published a volume containing the transcript of a public hearing held on the Guidelines as well as the correspondence received by the NIH Director on this matter prior to the release of the Guidelines in June.

III. Federal Interagency Committee on Recombinant DNA Research

The Interagency Committee on Recombinant DNA Research was created to address extension of the NIH Guidelines beyond the NIH to the public and private sectors. The Committee was convened by the Secretary of Health, Education, and Welfare with the approval of the President. Dr. Donald S. Fredrickson, Director of NIH, serves as chairman at the Secretary's request. The Interagency Committee is composed of representatives of Federal Departments and agencies that support or conduct recombinant DNA research, or that may do so in the future, and representatives of Federal Departments and agencies that have present or potential regulatory authority in this area. (The membership of the Committee is included in Appendix I.) The mandate of the Committee is to

(1) review the nature and scope of Federal- and private-sector activities relating to recombinant DNA research;

(2) determine the extent to which the NIH Guidelines may currently be applied to research in the public and private sectors;

(3) recommend, if appropriate, legislative or executive actions necessary to ensure compliance with the standards set for this research; and

(4) provide for the full communication and necessary exchange of information on recombinant-DNA-research programs and activities throughout the Federal sector.

Two meetings of the Committee were held in November 1976. The first of these, on November 4, was devoted to a review of the development of the NIH Guidelines for Research Involving Recombinant DNA Molecules. The Committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including Canada, the United Kingdom, most of Western Europe, the Scandinavian countries, Eastern Europe, the Soviet Union, and Japan.

In many countries appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries have acted to establish guidelines to govern the conduct of this research, including the United Kingdom and Canada. In the United Kingdom a parliamentary committee addressed the issue and indicated that work in this area should continue under appropriate safety conditions. Scientific advisory committees of international organizations, such as the World Health Organization, the International Councils of Scientific

Unions, and the European Molecular Biology Organization, have made similar recommendations.

The European Science Foundation, representing member nations from Western Europe and Scandinavia, has recommended to its members that they follow the guidelines of the United Kingdom. These guidelines are, in intent and substance, very similar to those of the National Institutes of Health. The NIH is currently working closely with the United Kingdom and the European Science Foundation to ensure a commonality of standards in the conduct of this research. Thus far, there has been very close cooperation and coordination among the various international and national scientific bodies, with a view to reaching a consensus on safety practices, programs, and procedures.

At the meeting of the Committee held on November 23, the Federal research agencies discussed their activities and possible roles in the implementation of the NIH Guidelines. All Federal research agencies endorsed the Guidelines to govern recombinant DNA research. At present, the NIH, the National Science Foundation, the Veterans Administration, and the U.S. Department of Agriculture are supporting or conducting such research. The NIH has 123 grants in which recombinant DNA research is involved. The National Science Foundation has 52 grants supporting such research in whole or in part. The Veterans Administration has eight projects. The Department of Agriculture and Agricultural Experiment Stations will soon have an estimate of the number of projects in their area. The Department of Defense, the National Aeronautics and Space Administration, and the Energy Research and Development Administration do not at present conduct such research, but all have endorsed the NIH Guidelines to govern future research should it be undertaken.

IV. Subcommittee Review of Existing Legislation

At the November 23 meeting of the Interagency Committee, the Federal regulatory agencies also reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of recombinant DNA research. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel. (See Appendix II for the membership of the Subcommittee.) The Subcommittee held meetings on December 13, 1976, and on January 11 and February 8, 1977.

The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in the United States (whether or not Federally funded) and would include at least the following regulatory requirements:

(1) review of such research by an institutional biohazards committee before it is undertaken,

(2) compliance with physical and biological containment standards and prohibitions in the NIH Guidelines,

(3) registration of such research with a national registry at the time the research is undertaken (subject to appropriate safeguards to protect proprietary interests), and

(4) enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much recombinant DNA laboratory research, but that no single legal authority or combination of

authorities currently exists that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements. The complete Subcommittee analysis is included in Appendix III. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed most deserving of detailed consideration:

(1) the Occupational Safety and Health Act of 1970 (Public Law 91-596),

(2) the Toxic Substances Control Act (Public Law 94-469),

(3) the Hazardous Materials Transportation Act (Public Law 93-633),

(4) Section 361 of the Public Health Service Act (42 U.S.C. Sec. 264).

The Occupational Safety and Health Act gives the Occupational Safety and Health Administration (OSHA) broad powers to require employers to provide a safe workplace for their employees. The term "employer" in the Act, however, is defined in such a way as to exclude States and their political subdivisions unless the OSHA standards are voluntarily adopted. Twenty-four States have adopted the standards, but twenty-six states are not subject to them. Further, the OSHA standards do not cover self-employed persons. For these reasons it was determined that OSHA at present could not regulate all recombinant DNA research.

The Environmental Protection Agency, under the Toxic Substances Control Act, is directed to control chemicals that may present an "unreasonable risk of injury to the health or the environment." The Subcommittee determined that the materials used in recombinant DNA research

would appear to be covered in most cases by the Act's definition of "chemical substance." Section 5 of the Act, however, explicitly exempts registration of chemical substances used in small quantities for the purposes of scientific experimentation or analysis. This represents a most serious deficiency, as the registration of activities was thought to be an essential element of any regulatory effort. Also, in order to meet the specifications of the Act, recombinant DNA research would have to be found to present "an unreasonable risk of injury to health or the environment."

The Hazardous Materials Transportation Act (HMTA) and Section 361 of the Public Health Service (PHS) Act give the Department of Transportation (DOT) and the Center for Disease Control (CDC), respectively, authority to regulate the shipment of hazardous materials in interstate commerce. Both the DOT and the CDC, in implementing these acts with respect to biological products, have essentially aimed at imposing labeling, packaging, and shipping requirements, and were found to be wanting for regulation of all recombinant DNA research.

The Environmental Defense Fund, in November 1976, petitioned the DHEW to regulate recombinant DNA research under Section 361 of the PHS Act. (The petition is included in Appendix IV.) The Subcommittee carefully reviewed this section, which is directed to organisms that are communicable and cause human disease. Thus, under this section, there would have to be a reasonable basis for concluding that the products of all recombinant DNA research may cause human disease and are communicable. Further, Section

361 does not apply to plants, animals, or the general environment. It was the conclusion of the Subcommittee that Section 361 lacked the requisite authority to meet all of the requirements set for the regulation of this research.

The Subcommittee also considered the authority of the CDC to license and control the operation of clinical laboratories under Section 353 of the PHS Act, but this provision was not considered to be applicable to research laboratories.

Other authorities of EPA under the Clean Air Act, the Federal Water Pollution Control Act, and the Resource Conservation and Recovery Act of 1976 were considered briefly and thought only to apply, if at all, to isolated aspects of recombinant DNA research. The authorities of the Food and Drug Administration (FDA) were also reviewed, but it was concluded that recombinant DNA research has not yet reached the stage of commercial application that comes under the FDA's jurisdiction. The regulatory powers of the U.S. Department of Agriculture (USDA) were also reviewed and found applicable solely to nonhuman animals and plants.

In summary, the group concluded that no single legal authority, or combination of authorities, currently exists which would clearly reach all recombinant DNA research in a manner deemed necessary by the Committee. Although there is existing authority that might be broadly interpreted to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge.

After completing an analysis of existing legislation, the Subcommittee on February 8, 1977, considered elements which might be

included in legislation to regulate recombinant DNA research. The Subcommittee referred the analysis of existing legislation and elements for new legislation to the full Committee at a meeting held on February 25, 1977. The full Committee adopted the report of the Subcommittee on existing legislation and agreed that new legislation was required.

V. Suggested Elements for Legislation

In considering the elements for legislation, the Committee reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research. Among congressional proposals reviewed were Senate Bill 621, "The DNA Research Act of 1977," introduced by Senator Dale Bumpers, and the companion measure introduced by Representative Richard L. Ottinger in the House (H.R. 3591). The Committee also noted the resolution (H. Res. 131) introduced by Representative Ottinger on January 19, 1977, requesting DHEW to regulate recombinant DNA research under Section 361 of the PHS Act.

Hearings held by State and local governments, including State legislatures, were among State and local activities reviewed. Recommendations for State regulation by the New York State Attorney General's Environmental Health Bureau, and for city regulation by the Cambridge (Massachusetts) City Council, were also considered.

Several committee representatives also reported on meetings with other interested parties whose views had been solicited on legislation to regulate recombinant DNA research. Those who were contacted include agricultural scientists, biomedical scientists, environmentalists, labor

unions, and private industry. At the request of the Chairman of the Committee, the Industrial Research Institute and the Pharmaceutical Manufacturers Association are surveying their member firms to determine the scope of the research efforts in the private sector. The Pharmaceutical Manufacturers Association has adopted the NIH Guidelines for safe conduct of this research.

In light of this review, the full Committee recommends that the following elements should be included in proposed legislation for the regulation of recombinant DNA research:

(1) Definitions:

"Recombinant DNA molecules" should be defined in a manner consistent with the NIH Guidelines.

Through an appropriate definition of the term "person," the legislation should cover any individual, corporation, association, Federal, State, or local institution or agency, or other legal entity.

"Secretary" should mean the Secretary of Health, Education, and Welfare.

(2) General requirements:

The legislation should bar any person from engaging in the production or use of recombinant DNA molecules in a State of the United States, in the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, American Samoa, Guam, the Trust Territory of the Pacific Islands, Wake Island, Outer Continental Shelf Lands as defined in the Outer Continental Shelf Lands Act, Johnston Island, or the Canal Zone, unless (a) such production or use is permissible under standards promulgated by the Secretary, (b) such production or use is in compliance with any such

standards, (c) the licensing requirements prescribed in the legislation have been satisfied, and (d) the registration requirements prescribed in the legislation have been satisfied.

The legislation should permit the Secretary to exempt activities from these requirements (a) where the activity is for specific commercial purposes found by the Secretary, after consultation with the regulating agency, to be regulated under other Federal law, or (b) where the Secretary determines that the activity poses no unreasonable risk to health or the environment.

(3) Standards:

The Secretary should be directed, as soon as practicable after passage of the legislation, to promulgate the NIH Guidelines for Research Involving Recombinant DNA Molecules as initial standards, with such clarifications and modifications as the Secretary determines to be necessary. Standards should assure, on the basis of the best currently available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee engages in the production or use of recombinant DNA molecules for an entire working lifetime.

The legislation should authorize the Secretary to modify and revoke any of these initial standards and to promulgate new standards.

The legislation should include an appropriate provision for judicial review.

(4) Licensure of laboratories:

The legislation should bar any person from engaging in the production or use of recombinant DNA molecules except at a facility licensed by the Secretary. A license should not be issued unless the Secretary determines that the facility will be operated in accordance with standards promulgated under the legislation and such other conditions as the Secretary deems appropriate.

The Secretary should have authority to exempt from the licensure requirement categories of activity which he determines pose no unreasonable risk to health or the environment. He should also, at his discretion, be able to utilize qualified accreditation or licensing bodies to assist him in carrying out this licensing function.

The legislation should have appropriate provisions for revocation, suspension, and limitation of licenses and for judicial review.

(5) Registration:

The legislation should bar any person from engaging in the production or use of recombinant DNA molecules unless the activity has been registered with the Secretary, provided that the Secretary should be able to exempt from the provisions of this section categories of production or use which he determines pose no unreasonable risk to health or the environment.

(6) Imminent hazards:

The Secretary should have authority to sue to enjoin the production or use of recombinant DNA molecules where he believes the activity would constitute an imminent hazard to health or the environment.

(7) Inspections, subpoenas, record-keeping, and reports:

The Secretary, in carrying out the legislation, should have authority to inspect facilities, make environmental measurements, conduct medical investigations, inspect medical records, issue subpoenas and citations, and require record-keeping and reports.

(8) Disclosure of information:

The legislation should provide that all records submitted to, or otherwise obtained by, the Secretary or his representatives under the legislation shall be available to the public upon request, except (a) information now exempt from disclosure under the Freedom of Information Act, and (b) other information the disclosure of which would cause the loss of proprietary rights.

At the time of request, persons who have submitted records should be given an opportunity to identify those portions which they believe to be excepted from disclosure under the preceding paragraph. The Secretary should not release such portions unless (a) he has found the portions so identified not to be excepted and has given the submitter advance notice of this finding and an opportunity to rebut it, or (b) the public need to know so outweighs the interest of the submitter as to require release. Where the Secretary releases records or portions thereof because of the public need to know, he should notify the submitter, setting forth the urgent health or environmental needs which serve as the basis for his action.

(9) Coordination:

The legislation should provide specifically for interagency coordination in setting standards and avoiding duplicative requirements.

(10) Preemption:

The legislation should specifically preempt all State and local laws regulating the production or use of recombinant DNA molecules; except that where a State passes a law imposing requirements identical to those contained in the Federal legislation, the Secretary should have discretion to enter into an agreement with the State to carry out the Secretary's responsibilities under the legislation.

(11) Enforcement:

The legislation should contain provisions for enforcement and sanctions.

(12) Employee rights:

The legislation should contain protections for employees who cooperate in the enforcement of these provisions.

(13) Sunset:

The legislation should remain in effect for a period of five years from the date of enactment, unless further action is taken by Congress.

VI. Suggested Elements for Legislation: Committee Analysis

In considering these elements for proposed legislation, a number of issues were raised and discussed by the Committee. The issues that the Committee considered of importance are described below.

(1) Definition of the Term "Secretary":

The Committee considered the appropriate locus in the Government for the regulation of the use and production of recombinant DNA molecules. It determined that the Department of Health, Education, and Welfare

is the appropriate locus in light of

(a) NIH's role as a lead agency in setting the standards,

(b) the petition by the Environmental Defense Fund to DHEW to issue regulations in this area,

(c) the congressional proposals that placed regulatory responsibility in DHEW, and

(d) the experiences of DHEW's Center for Disease Control in regulating infectious agents, and of its Bureau of Biologics (FDA) in licensing the production of biological products, in close cooperation with other Federal Departments and agencies.

This recommendation was formally approved by all members of the Committee. The Committee also urges close cooperation and coordination in DHEW between the NIH and regulatory agencies to ensure effective implementation of the standards set for this research.

(2) The Scope of Regulation:

The Committee reviewed at great length the nature and scope of regulation. Consideration was given to regulation of all laboratory research where hazardous or potentially hazardous substances were employed. Dr. Fredrickson reviewed the activities of committees at the NIH other than the Recombinant DNA Molecule Program Advisory Committee which have been created to study and recommend, if necessary, safety standards for other research involving actual or potential biohazards.

There was general Committee agreement that, for the present, legislation should be restricted to recombinant DNA techniques, allowing for sound administrative and scientific expertise in developing safety standards

and regulation in other areas. The Committee considered whether, in the proposed legislation, the regulations should be limited to research. As noted above in the analysis of existing legislation, no current single, legal authority reaches all research under requirements set for regulation by the Committee. However, the Occupational Safety and Health Administration and the Environmental Protection Agency do have authority for regulation of commercial applications of recombinant DNA molecules.

Regulation of research alone presents a problem because of the difficulty in determining the border between research and pilot production. Therefore, the Committee recommends that regulation cover the production or use of recombinant DNA molecules. Such language would include research activity, and makes immaterial any consideration of whether a given activity constitutes research, pilot production, or manufacture. The Committee recommends that the Secretary, in consultation with appropriate regulatory agencies, be allowed to determine the nature of the activity and should defer to a regulatory body he determines is better empowered and equipped to deal with it.

The Committee also recommends as a suggested element for legislation a "sunset provision" for the regulatory authority. This provision is intended to mandate a review of regulation in light of accumulated scientific and safety information. This provision, the Committee wishes to emphasize, does not refer to records and other data relevant, for example, to medical, occupational, or environmental surveillance.

(3) Registration:

There was general agreement by the Committee that registration of projects and other activities involving the use or production of recombinant

DNA molecules was an important element of regulation. It was the consensus of the Committee that registration should occur prior to the initiation of the project, but that approval before commencing the project should not be required. Further, the Committee recommends that the Secretary have the authority to exempt certain classes of projects from this requirement.

(4) Licensure of Facilities:

It was the consensus of the Committee that the licensure provision should apply only to facilities, and that the facility would, under the terms of its license, accept responsibility for the particular activities and individuals at the facility. The Committee concluded that licensure of the facility and registration of projects would meet the needs for safety monitoring without extension of licensure to the projects themselves. The Committee discussed the possibility of revoking a license for serious and willful violations of the regulations. There was concern expressed that revocation was a very punitive measure, but it was agreed that the Secretary may wish to consider it for serious violations of the standards.

(5) Disclosure of Information:

It was the scientific community that brought to public attention potential hazards of recombinant DNA research, and the NIH Guidelines, in that spirit, promote disclosure and dissemination of scientific and safety information. The Committee urges full disclosure to the appropriate regulatory body of all relevant safety and scientific information on the use or production of recombinant DNA molecules. However, the Committee

recognizes the important world-wide commercial potential of recombinant DNA molecules in medicine, agriculture, and other areas of science and technology. It believes that the potential commercial uses of recombinant DNA techniques require that information of a proprietary nature and patent rights be given appropriate protection from disclosure by the regulatory agency receiving such information. Some Committee members expressed concern that universities and inventors with limited resources may be unable to adequately protect data of a proprietary nature if the regulatory agency acts to disclose such information. The regulatory agency should consider the burden of its action on these inventors.

(6) Preemption of State/Local Laws:

The potential hazards posed by the use of recombinant DNA techniques extend beyond the local to the national and international levels. Therefore, the Committee recommends that a single set of national standards must govern and that, accordingly, local law should be preempted to ensure national standards and regulations. The Committee, however, took into account the activities at the State and local levels on regulation of recombinant DNA research. It was agreed that if a State passes a law imposing requirements identical to those contained in the Federal legislation, then the Secretary may enter into an agreement with the State to utilize its resources to assist the Secretary in carrying out his duties.

(7) Inspection and Enforcement:

The Committee proposes that there be inspection and enforcement requirements to ensure that standards are being met. In order to protect

the public health from an imminent potential hazard, the Committee also recommends that the Secretary have authority to enjoin the use or production of recombinant DNA molecules when he deems it necessary.

The Committee also reviewed the question of civil liability in the event of injury to humans or the environment. It believes that actions for damages should be left to State and local law. It is concerned that the inclusion of standards for strict liability as proposed in S. 621 could place a severe constraint on the ability of an institution to obtain liability insurance. It was predicted that, without insurance, institutions might have to terminate their research efforts unless national legislation were passed to indemnify them against adverse judgments.

(8) Interagency Cooperation:

Because of the wide potential use and production of recombinant DNA molecules and the need for uniform development and implementation of standards, the Committee recommends that mechanisms be established by the Secretary to ensure cooperation and coordination among appropriate Federal Departments and agencies. The National Institutes of Health is developing appropriate liaison between its Recombinant DNA Molecule Program Advisory Committee and relevant Federal research agencies, such as the Department of Agriculture, the National Science Foundation, and the Energy Research and Development Administration.

VII. Future Agenda

Pending action on possible legislation, the Committee stands ready to assist DHEW or whatever agency is made responsible for regulation of activities involving the use or production of recombinant DNA molecules.

For example, research agencies on the Committee are working in coordination with the National Institutes of Health and its Recombinant DNA Molecule Program Advisory Committee on setting standards and certifying new host-vector systems. The research agencies have also been developing a registry of projects supported by Federal funds. The survey being taken in the private sector by the Pharmaceutical Manufacturers Association and the Industrial Research Institute will provide data on the industry, in anticipation of registration under a new law.

The Committee will consider suggestions by the representatives from the State Department concerning further means to ensure international control in the use and production of recombinant DNA molecules. At present, there is voluntary coordination and cooperation among national scientific bodies. The Biological Weapons Convention is considered by the State Department to prohibit development, production, or stockpiling of recombinant DNA molecules for purposes of biological warfare. The Committee will review whether other measures need to be considered for international control.

The Committee will also be reviewing current Federal policies on the matter of patenting recombinant DNA inventions and other matters of concern that may need to be addressed before the Committee concludes its business and files a final report.

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Appendix III

REGULATION OF RECOMBINANT DNA
RESEARCH IN LABORATORIES

BACKGROUND

On December 20, 1976 a meeting was held at NIH of attorneys 1/ from the Departments of Justice, Agriculture, HEW, Labor, and Transportation and the Environmental Protection Agency, for the purpose of assessing whether legislative authority currently exists for imposing at least the following regulatory requirements on all recombinant DNA laboratory research in the United States (whether or not Federally funded):

1. Review and approval of such research before it is undertaken by a local biohazards committee.

2. Compliance with the physical and biological containment standards and prohibitions in the NIH Guidelines.

3. Registration of such research with a national registry at the time the research is undertaken (subject to appropriate safeguards to protect proprietary interests).

4. Enforcement of the above requirements through monitoring, inspection, and sanctions.

It was generally conceded for purposes of the discussion that these requirements could be imposed by funding agencies on Federally conducted or supported research, and primary attention was therefore directed to whether authority now exists to mandate these requirements

1/ A list of attendees is attached.

for all recombinant DNA laboratory research without regard to the source of funding.

SUMMARY CONCLUSION

In summary, the group concluded that, while present law would permit imposition of some of the above requirements on much recombinant DNA laboratory research, no single legal authority or combination of authorities currently exists which would clearly reach all such research and all requirements. Although there is existing authority which could be interpreted to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge.

LAWS CONSIDERED

In reaching this concensus, discussion centered on the following laws:

1. The Occupational Safety and Health Act of 1970 (Public Law 91-596).
2. The Toxic Substances Control Act (Public Law 94-469).
3. The Hazardous Materials Transportation Act (Public Law 93-633).
4. Section 361 of the Public Health Service Act (42 U.S.C. §264).

Authorities of EPA under the Clean Air Act, the Federal Water Pollution Control Act, and the new Resource Conservation and Recovery Act of 1976, were mentioned in passing, but it was felt they would apply, if at all, only to isolated aspects of recombinant DNA research carried out in the laboratory. The FDA was also discussed briefly. However, inasmuch as recombinant DNA research has not yet reached the stage where it has practical applications in fields regulated by FDA, it was agreed that FDA probably does not have authority to impose requirements on such research. The Department of Agriculture's regulatory powers were also touched upon, but not considered in depth because they relate solely to certain forms of non-human animal life and plants.

DEPARTMENT OF LABOR

Of the four statutes on which discussion centered, primary attention was directed to the Occupational Safety and Health Act and the Toxic Substances Control Act, because each on its face would give broad powers to the administering agencies.

The Occupational Safety and Health Act, administered by the Occupational Safety and Health Administration (OSHA) in the Department of Labor, requires every employer to: (1) furnish to each of its employees ". . .employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death

or serious physical harm. . ." to the employees, and (2) ". . .comply with occupational safety and health standards promulgated under this Act." The aforesaid Act gives OSHA broad power to enforce compliance with the Act, including a right of entry, authority to require record-keeping and reports, and sanctions. In addition, the Act specifically directs that trade secret information shall be treated by OSHA as confidential.

The term "employer" is defined in such a way, however, as to exclude States and their political subdivisions, as well as the United States. The Act contains a separate provision requiring Federal agencies to follow OSHA standards, but States and their subdivisions are subject to OSHA requirements only by voluntary agreement on the part of each State. Only 24 States have so agreed and there is no immediate expectation that this number will increase. Hence, such organizations as State universities in 26 States are not subject to OSHA requirements.

In addition, OSHA has authority only in cases where an employment relationship exists. Hence, it could not prevent a self-employed person from conducting recombinant DNA research as long as no employees would thereby be affected.

Turning to the requirements themselves, since recombinant DNA research does not necessarily present a "recognized hazard" with respect to all areas of that research, and because of possible litigation problems in proving a recognized hazard, the imposition of all NIH Guidelines on employers can best be achieved by adopting them

as standards, in accordance with detailed rulemaking procedures spelled out in the Act. Among the policy questions which would have to be resolved in contemplating this step are: (1) whether OSHA would agree to an outright ban of some activities since it has never in the past actually prohibited a total activity, and (2) whether OSHA should give priority to establishment of these standards over others that have been awaiting promulgation, taking into account the statutory test of ". . . urgency of the need for mandatory safety and health standards for particular industries, trades, crafts, occupations, businesses, workplaces or work environments."

ENVIRONMENTAL PROTECTION AGENCY

The Toxic Substances Control Act (TSCA), primarily administered by EPA, was enacted in October 11, 1976, effective January 1, 1977. Section 6 of the TSCA states in part that:

> "If the Administrator [of EPA] finds that there is a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents or will present an unreasonable risk of injury to health or the environment, the Administrator shall by rule apply one or more of the following requirements to such substance or mixture to the extent necessary to protect adequately against such risk using the least burdensome requirements:
>
> (1) A requirement (A) prohibiting the manufacturing, processing, or distribution in commerce of such substance or mixture, or (B) limiting the amount of such substance or mixture which may be manufactured, processed, or distributed in commerce.

> (2) A requirement--
>
> (A) prohibiting the manufacture, processing, or distribution in commerce of such substance or mixture for (i) a particular use or (ii) a particular use in a concentration in excess of a level specified by the Administrator in the rule imposing the requirement, or
>
> (B) limiting the amount of such substance or mixture which may be manufactured, processed, or distributed in commerce for (i) a particular use or (ii) a particular use in a concentration in excess of a level specified by the Administrator in the rule imposing the requirement."

The TSCA contains inspection and penalty provisions, and a section limiting disclosure of data.

NIH scientists agree that materials used in recombinant DNA research in the laboratory, and the immediate products of such research, would appear to be covered in most cases by the definition of "chemical substance" in the TSCA. The term "manufacture" is defined as meaning ". . .to import. . .produce, or manufacture." The term "manufacture" does not normally connote scientific experimentation in the laboratory. Thus, some question could be raised as to whether section 6 has any applicability to such research. However, another section of the TSCA (section 5), which requires manufacturers to give EPA advance notice of plans to manufacture a new chemical substance, contains an exemption from the notice requirement for ". . .manufacturing or processing of any chemical substance. . .only in small quantities. . .solely for purposes of. . .scientific experimentation or analysis. . . ." The wording of this provision would seem to indicate that scientific

experimentation constitutes manufacturing under the TSCA, 2/ and also the absence of a similar provision in section 6 creates a negative implication that section 6 applies to such experimentation. Nevertheless, this is an area of some controversy that could well lead to future litigation in the event EPA attempts to regulate laboratory research.

In the event EPA can regulate recombinant DNA laboratory research under the TSCA, it can do so only if it finds such research presents an "unreasonable risk of injury to health or the environment." This offers another area of potential controversy should EPA attempt to regulate all such research through this mechanism. 3/

The most serious deficiency in the TSCA, as a vehicle for regulation of recombinant DNA laboratory research, is presented by section 5, noted above, which requires manufacturers to notify EPA when they intend to manufacture a new chemical substance. As has already been indicated, scientific experimentation is specifically exempted from this requirement. Since section 5 deals directly with notice, and in effect registration,

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2/ A point supported by the fact that section 5 has a separate definition of "manufacture" solely for purposes of that section, which is limited to manufacture "for commercial purposes." The quoted phrase does not appear in the more general definition applicable to section 6.

3/ On the other hand, the TSCA authorizes any person to commence a civil action to compel EPA to perform any act or duty under the TSCA which is not discretionary. In some cases, this could lead to litigation regardless of what course of action EPA adopts.