and provides an exemption for such experimentation, it is doubtful that section 6 could be utilized to require registration. Otherwise, the intent of Congress in enacting the exemption would be undermined.

DEPARTMENT OF TRANSPORATION
AND
CENTER FOR DISEASE CONTROL, HEW

The Hazardous Materials Transportation Act (HMTA) and section 361 of the PHS Act give the Department of Transportation and the Center for Disease Control, HEW, respectively, authority to regulate shipment of hazardous materials in interstate commerce. 4/ The HMTA authorizes the Secretary of Transportation to issue and enforce regulations governing any safety aspect of the transportation of hazardous materials, including but not limited to packing, repacking, handling, labeling, mailing, placarding, and routing, and the manufacture, fabrication, marking, maintenance, reconditioning, repair, or testing of packages or containers represented, marked, certified, or sold by certain persons for use in the transportation of certain hazardous materials. 5/

Section 361 authorizes the Secretary of HEW to ". . .make and

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4/ Including intrastate commerce that affects interstate commerce.

5/ In the Federal Register for November 26, 1976, at page 52086, the Department of Transportation has asked for public comment as to whether it should expand the definition of "etiologic agents" in DOT regulations". . .to include biological materials (such as recombinant DNA) used in or derived from genetic studies."

registration requirement may be found in the Federal Insecticide, Fungicide, and Rodenticide Act (Public Law 92-516), which sets forth a detailed procedure for registration of pesticides.

2. On the issue of protection of proprietary information submitted to the Government as part of the registration process, while the Freedom of Information Act (FOIA) provides in general that records in the possession of Government agencies are available to the public upon request, the FOIA does not apply to, among other things, ". . .trade secrets and commercial or financial information obtained from a person and privileged or confidential. . ." (exemption 4). Moreover, 18 U.S.C. §1905, part of the Federal criminal code, makes it illegal for a Government employee to disclose ". . .to any extent not authorized by law any information coming to him in the course of his employment. . . which information concerns or relates to the trade secrets, processes, operations, style of work, or apparatus. . .of any person, firm, partnership, corporation, or association. . . ." In Charles River Park "A," Inc., et al. v. The Department of Housing and Urban Development, et al., a 1975 decision, the United States Court of Appeals for the District of Columbia held that, where an agency record is exempt from FOIA disclosure by virtue of exemption 4 and the record contains information covered by section 1905, the record would be subject to the prohibition against disclosure in section 1905.

4. It was the general concenaus of all attorneys present that, to the extent no statutory basis existed for regulating non-Federally funded recombinant DNA laboratory research, this could not be achieved by Executive Order of the President. 6/

5. There was a brief discussion of whether, if agency X could regulate one type of recombinant DNA research and agency Y could regulate another type, agency Y could delegate its authority to agency X so that there could be comprehensive regulation by one agency. No conclusion was reached as to whether such an arrangement was legally barred. However, the only instance of this which any attorney could recall took place in the context of a specific statutory provision allowing the agency (the Customs Service) to do so.

6/ Particularly insofar as the entity conducting the research received no Federal funds for other recombinant DNA research.

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Appendix IV

Environmental Defense Fund

1525 18th Street, NW, Washington, D.C. 20036 • 202/833-1484

November 11, 1976

The Honorable David Mathews
Secretary
Department of Health, Education & Welfare
South Portal Building, Room 615 F
200 Independence Avenue, S. W.
Washington, D. C. 20201

Dear Dr. Mathews:

The Environmental Defense Fund and the Natural Resources Defense Council hereby submit to you a petition concerning the regulation of recombinant DNA research and technology. We would very much appreciate your giving this matter prompt attention.

Enclosed also are copies of letters from Dr. Robert L. Sinsheimer of the California Institute of Technology and Mr. Alan McGowan, President, Scientists' Institute for Public Information.

Sincerely yours,

Burke K. Zimmerman

Burke K. Zimmerman, Ph.D.
Staff Scientist
Environmental Defense Fund

OFFICES IN: EAST SETAUKET, NY (MAIN OFFICE); NEW YORK CITY (PROGRAM SUPPORT OFFICE); WASHINGTON, DC; BERKELEY, CALIFORNIA; DENVER, COLORADO
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hazards that might arise in the conduct of such research. The Guidelines do not address what I perceive as the larger, potential ecological and evolutionary hazards implicit in this research. Nor do the Guidelines address the potential significance of the availability of this new technology - developed by scientists to solve their own scientific problems - to other diverse sectors of our society, which may wish to use it for their own ends.

I believe the Guidelines do not provide sufficient recognition of the fact that we are here creating novel living organisms - unprecedented in the evolutionary order. As living organisms they are self-perpetuating and destined to their own individual evolution. I do not believe we can predict the properties of these organisms - created by the fusion of genes from disparate species - or their subsequent evolution, or their impact, present and future, on the existent biosphere. We do not know that there is a hazard here but neither do we know there is not. If such hazard exists or develops it will be in this instance uniquely irreversible. I believe a thoughtful reformulation of the Guidelines to take these circumstances into account would be most appropriate.

Sincerely yours,

Robert L. Sinsheimer

Robert L. Sinsheimer
Chairman

November 5, 1976

Public hearings are absolutely essential in this process of discussion and debate. The Scientists' Institute for Public Information wholeheartedly supports the petition of the Environmental Defense Fund and the Natural Resources Defense Council for the conduct of public hearings on recombinant DNA research.

Sincerely yours,

Alan McGowan
President

AM:m
cc: Dr. Karim Ahmed
Natural Resources Defense Council
15 W. 44th St.
New York, New York 10036

Recombinant DNA technology permits the creation of organisms or viruses with an unprecedented genetic make-up which may have the potential of causing grave and irreversible harm to humans and the environment. The extent of our current knowledge does not allow us to predict all of the possible results of experiments involving the manipulation of genes. Because most of the present and proposed recombinant DNA research and technology involves the genetic modification of bacteria or viruses, there exists the potential danger of creating a highly deleterious communicable infectious agent that could be introduced into and spread among laboratory workers and/or the general population (see infra, pp. 9 - 12).

Recognizing the potential hazards inherent in recombinant DNA research, the National Institutes of Health (hereinafter "NIH") on 23 June, 1976 promulgated guidelines [1/] which prohibit certain experiments where the potential risks to human health are deemed to be particularly high, and require a graded set of safety procedures for all other experiments (see 41 Fed. Reg. No. 131, part II, pp. 27902-27943, July 7, 1976). NIH also filed a draft environmental impact statement (hereinafter the "impact statement") on 1 September, 1976, which sets forth some of the possible dangers of recombinant DNA research and technology (see 41 Fed. Reg. No. 176, pp. 38425-44, Sept. 9, 1976). NIH indicated that the guidelines are not a final statement of public policy on

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[1/] The petitioners take no position at this time concerning the adequacy of the safety standards set forth in these guidelines.

United States; and (3) the present NIH guidelines be promulgated immediately as interim relief regulations governing all parties conducting or supporting such research.

This document includes:

I. A description of the scope of this petition (p. 4);

II. A description of the petitioners (p. 6);

III. A discussion of the need to control recombinant DNA research and technology in the interest of public health (p. 7);

IV. A discussion of the legal basis for the regulation of recombinant DNA research and technology by the Secretary of HEW (p. 13); and

V. A description of proposed relief (p. 15).

I. Scope of the Petition

By this petition EDF and NRDC seek interim and final regulations which will protect the public from the potential hazards of uncontrolled recombinant DNA research and technology.

In this petition the term "recombinant DNA research and technology" means all procedures in which DNA fragments from two or more different organisms or viruses which do not normally recombine in nature are recombined in the laboratory and inserted into a living host cell or organism in such a way as to alter its genetic make-up. This includes, but is not limited to, any experiments involving transportation of or commercial use of recombinant

II. Petitioners

Petitioner Environmental Defense Fund, Inc., is a not-for-profit public-benefit membership corporation organized and existing under the laws of the State of New York. Its principal office and place of business is located at 162 Old Town Road, East Setauket, New York. It also maintains offices in Washington, D.C.; New York, New York; Denver, Colorado; and Berkeley, California. EDF has a nationwide membership of over 40,000 persons, composed of scientists, educators, lawyers, and other citizens dedicated to the protection of the environment and the wise use of natural resources. Many of these persons and their children will be subjected to the increased risk of adverse health effects discussed in at pp. 9 - 12, infra, if the Secretary does not adopt effective regulations controlling the relevant procedures. By its activities, EDF seeks the preservation and restoration of environmental quality and the protection of the country's natural resources on behalf of the general public. Its objectives include combining "the best scientific findings with the most appropriate social action discovered by the social sciences and legal theory in order that practical decisions shall be made which shall best promote a quality environment." (EDF By-laws, Art. 1:2(d)).

Petitioner Natural Resources Defense Council, Inc., is a not-for-profit, tax-exempt corporation organized under the laws of the State of New York, with offices at 15 West 44th Street, New York, New York; 917 15th Street, N.W., Washington, D.C.; and 2345 Yale Street, Palo Alto, California. NRDC is a national organization dedicated to environmental protection, including

from potentially hazardous novel organisms which might arise from such research.

Addressing these questions, NIH formed a committee (the Recombinant DNA Molecule Program Advisory Committee) composed of scientists, many of whom were directly involved in recombinant DNA research, to draft guidelines governing the conduct of recombinant DNA research and establish safeguards to protect the public and the environment from potential hazards. The guidelines, applying only to NIH supported research, were made public June 23, 1976. Recognizing the far-reaching environmental consequences which could result if infectious or otherwise dangerous organisms able to compete successfully with existing organisms were to be produced by recombinant DNA research, and in response to requests from the public, NIH prepared a Draft Environmental Impact Statement which was released September 1, 1976.

The Impact Statement, in discussing the alternative of "no action," unambiguously concludes that regulation of recombinant DNA research and technology is essential for the protection of the public:

> "the 'no action' alternative would greatly increase the probability that possible hazardous organisms would be released into the environment. . . . It is concluded that the 'no action' alternative would not afford adequate protection of laboratory workers, the general public, and the environment from the possible hazards described in section IV-C-1." (at p. 48).

Some of the possible hazards which could arise either directly or as an inadvertent result of recombinant DNA research are discussed in Section IV-C of the Impact Statement. One may

In view of the ubiquitous nature of E. coli, the fact that all strains including K-12 already have the capacity for human infection, and E. coli's ability to exchange genetic material with other bacteria, the deliberate genetic modification of even "weakened" strains of E. coli poses a potentially serious threat to human health.

2. DNA can be taken from organisms that produce toxins (e.g. botulinum) creating the possibility that the host organism, which occupies a different ological niche, will acquire the ability to produce tha toxin. This would be particularly serious if such genes were expressed in strains of E. coli capable of colonizing the human colon.

3. Genes which code for resistance to antibiotics are transferred by some recombinant DNA experiments to strains of bacteria that were not previously resistant.

4. The animal virus on which the most genetic information is available is simian virus 40 (SV-40), which produces tumors in some animals and infects humans, although apparently with no pathological symptoms. However, the genetic basis for the virus causing tumors in monkeys but not humans is not understood. Therefore, the possibility exists that even an apparently innocuous modification of SV-40 DNA could render the virus tumorigenic or otherwise pathogenic to humans, thus creating a serious hazard to human health. Yet it is SV-40, and polyoma

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In the context of auto-immune disease, however, the gene specifying any foreign protein must be considered potentially harmful.

7. The expression of even a "normal" metabolic enzyme in human, animal or plant cells which was not under the control of the cell's normal complex regulatory mechanism, could lead to severe metabolic disruptions and an ensuing disease state, similar to existing cases of metabolic disease where the defect is in a regulatory gene, rather than once coding for a specific enzyme.

Both the NIH guidelines and the Impact Statement recognize that humans harboring or infected by bacteria or viruses containing recombinant DNA may, under certain conditions, suffer a variety of serious adverse health effects. If such modified bacterial or viral agents can survive and propagate outside the laboratory and thus produce new identical organisms capable of producing infection and/or toxic effects on human beings, there exists the potential for a "communicable disease" within the meaning of Section 361 of the Public Health Service Act (42 U.S.C. §264). (see Section II above). Because some of the organisms created by recombinant DNA research have never existed before, the health and environmental effects of such novel microorganisms are inherently unpredictable. Nevertheless, the danger of the creation of a potentially serious communicable disease organism makes it incumbent upon the Department of Health, Education and Welfare to exercise its statutory authority and take whatever regulatory measures are necessary to protect the public health.

> diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession . . ."

It further provides that:

> for purposes of carrying out and enforcing such regulations, the [Secretary] may provide for such inspection, . . . disinfection . . . and other measures, as in his judgment may be necessary.

Recombinant DNA research and technology could create novel infectious agents or increase the virulence and range of existing infectious agents. The Draft Environmental Impact Statement recognizes that recombinant DNA activities could produce microorganisms that cause disease in laboratory workers and the general public. In describing the Guidelines the Draft EIS states:

> "The emphasis on protection of laboratory workers from infection reflects the fact that laboratory workers are the persons at the greatest risk of infection and that the most likely route of escape of possibly hazardous agents from the laboratory is the laboratory worker." (41 Fed. Reg. 38432)

In describing the highest level of physical containment required by the Guidelines to the Draft EIS states that such facilities are:

> "designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease."

The kinds of disease which may be caused by recombinant DNA activities are described in Section III of this petition (<u>infra</u> at pp. 9 - 12).

The Secretary has defined "communicable disease" in regulations promulgated under Section 361 to govern the importation of animals and establish drinking water standards. For the purposes of both these sets of regulations a communicable disease is "An illness due to an infectious agent or its toxic product . . ." transmitted by persons, animals, plants or the inanimate environment. (42 C.F.R. §§71.1(b), 72.1(b)). These regulatory definitions of communicable

3. As interim relief, regulations which make the NIH guidelines binding on all parties engaged in recombinant DNA research and technology.

This relief is necessary to insure that the public has an adequate opportunity to participate in the decision of whether and under what conditions recombinant DNA research and technology should be permitted and to insure that the protection provided the public by the NIH guidelines is immediately extended through the application of the NIH guidelines to all recombinant DNA research and technology.

A. The Need for a Legislative-Type Hearing

The NIH guidelines, which at present are the only statement of government policy on recombinant DNA research and technology, are the product of the deliberations of scientists who are now conducting recombinant DNA research. The NIH guidelines had their origin in the Asilomar Conference held in Pacific Grove, California in February 1975. Many of the participants at that conference were the foremost molecular biologists from all over the world. The NIH Recombinant DNA Molecule Program Advisory Committee translated the recommendations of that conference into concrete proposals which became the NIH guidelines. The first opportunity the public had to participate in the regulation of recombinant research was in February of 1976 when the draft guidelines were released for public comment, and the Advisory Committee to the Director of NIH[1/] held an open meeting.

1/This committee should not be confused with the NIH Recombinant DNA Molecule Program Advisory Committee, which drafted the guidelines, but is one assembled early in 1976 from representatives of science, law, teaching, public interest groups, students, etc. to advise the director of NIH on the correctness or shortcomings of its efforts to regulate recombinant DNA research.

request was denied in an administrative decision by the director of NIH and not even submitted to the advisory committee for further debate in its April 1-2, 1976 meeting in which final revisions of the guidelines were made. At this meeting, all of the outside comments had been distilled down to ten typewritten pages of questions for the consideration of the recombinant DNA advisory committee, the same committee which had drafted the working version prepared early in 1976. Except for relatively minor changes in wording, the committee dealt summarily with the questions from the public, and the final version of the guidelines did not differ significantly from the version prepared prior to public input.

The legislative-type hearing should consider the following issues which were not adequately considered in the NIH proceedings which led to the promulgation of the guidelines:

(a) Whether or not recombinant DNA research on <u>any</u> level should be permitted at this time in view of our present state of knowledge.

(b) If some areas are to be permitted, what are they and what precautions are necessary to adequately protect the public and the environment? For example, what degree of physical containment should be considered adequate in light of human fallibility?

procedures for others. The hazards of recombinant DNA research and technology are no different if the research is being conducted by scientists employed by private corporations rather than the NIH. The risk that necessitated regulation of NIH grantees necessitates regulation of other research and technology. The need for regulation of all parties conducting recombinant DNA research is particularly great because even one release of a hazardous genetically altered bacterium, virus or plasmid could cause widespread illness or disruption of the environment.

C. Interim Relief

During the period before the hearing is held and final regulations are promulgated the public will be exposed to the potential hazards of recombinant DNA research and technology not now subject to NIH guidelines. Individuals who do not receive NIH grants or work for NIH are not effectively restrained from conducting any of the experiments which NIH deemed so dangerous that they should not be conducted at all. Nor are scientists not now covered by the guidelines required to practice physical and biological containment of organisms with recombinant DNA molecules. To protect the public until final regulations are promulgated, EDF and NRDC request that the Secretary immediately promulgate regulations which make the NIH guidelines binding on all parties engaged in recombinant DNA research and technology.

Dr. FREDRICKSON. 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.

The committee reviewed at great length the nature and scope that potential legislation should have. There was general agreement that legislation should be restricted to the use of recombinant DNA techniques.

Regulation of the research aspects of recombinant DNA techniques presents a serious problem because of the difficulty in determining the border between research and pilot production. Therefore, the committee recommended that regulation cover the production or use of recombinant DNA molecules. Such language would include research activity, and make immaterial possible concerns whether a given activity was actually research, pilot production, or manufacture.

The consensus of the committee is that registration of projects involving the use or production of recombinant DNA molecules is 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 meet the needs for safety monitoring rather than licensure or registration of individuals engaged in research.

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 insure national standards and regulations.

A number of other recommendations are made, and I can discuss them further if you should have any questions. I would like to emphasize that the work of the Interagency Committee has been done in a most cooperative and helpful way. It is paramount to legislation which may place authority of regulation of these activities in the Department of HEW, that the Department continue to cooperate and coordinate with relevant Federal departments or agencies in this important matter.

In conclusion, Mr. Chairman, I think this much is clear: The international and the 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 exist everywhere for the use of these techniques. And the question being debated now everywhere is how this is to be accomplished.

In the United States, as we have discussed, this question has attracted far more public attention than in other countries. A number of local jurisdictions or States have been engaged in either actions or debates.

I believe that it is a common desire that effective Federal standards shall soon extend over all use of these techniques within this country, and that such standards and their implementation within the United States will form a useful example and a helpful basis for effective international use of sueh techniques.

There are other aspects, of course, which are somewhat more artificial: Cell fusion experiments, mutagenesis, which is induced in the laboratory, changes in DNA material within single organisms; other aspects of recombination such as you have referred to.

I suppose nothing, however, seems so stark or dramatic as a change in man's capabilities for affecting the genetic material of any species. In the eyes of many people, we have a new ability to leap over a barrier that may have existed since the beginning of evolution. Whether such a barrier is absolute, or actually has been crossed in nature many times in millions of years prior to this, really represents one of the great unanswered questions.

Chairman THORNTON. Do you have a view with regard to that, Dr. Fredrickson?

Dr. FREDRICKSON. Well, not professing to know for sure, I lean toward the side of the evidence that suggests some recombination between, say, bacterial DNA and that of the higher animals in which bacteria may live has probably occurred. But it has occurred in a fairly low order of probability.

Given the length of time we are talking about, I suspect that nature has already tried out many recombinations long before our time.

Chairman THORNTON. I have wondered if this might have happened.

Dr. FREDRICKSON. There are bits of evidence that supports this view. One would like to know, however, much more about this, and I hope that will be part of the new knowledge that can be obtained as these techniques are used.

But, to answer your question more fully, I think that there is a dramatic difference involved in recombinant techniques, a difference which allows us little of the lengthy experience that has occurred with other experiments in recombination over many, many years, a lack of experience which makes us unable to predict precisely what may be the benefits or the hazards.

In attempting to deal with this delicate question, it is well that we have confined ourselves to a very narrow segment, because attempting to regulate research is very difficult. Attempting to do it too broadly at once, or in a clumsy fashion, might well be an extraordinarily destructive exercise.

At the same time, I think that as we pursue this effort we do have to set in motion—and we have at NIH, and so have other bodies—examination of other aspects of genetic recombination, to be sure that we understand as well as we can the hazards of these, and whether or not we may need to issue some kind of guidelines for the conduct of these techniques as well.

Chairman THORNTON. You hit upon one other question that I would like to explore very briefly before recognizing Mr. Brown for questions, and that is the difficulty of enforcement of regulations, and the need for having an internationally accepted standard.

Obviously, if you do not have some agreement between nations all of which are capable of conducting this kind of research, presumably a Gresham's law might apply, where most of the research would go on in the nations which had the lowest standards.

What mechanisms do you think would be necessary in order to have this type of international standard adopted and enforced?

The other difference may be, as I indicated, that we may by this means be able to create recombinations that simply would not otherwise have occurred in nature, through any other type of technique.

Mr. BROWN. It's broader then than what we do by the normal breeding processes to alter genes?

Dr. FREDRICKSON. It is potentially broader, Mr. Brown. It will depend a great deal, of course, on whether recombinations reintroduced into a host are actually expressed.

Mr. BROWN. Well, let's take another example. Over the past generation we've experimented a great deal with the preparation of toxic chemicals aimed at affecting biological life, as described initially by Rachel Carson in "Silent Spring," and now we see the effect it was having on the biosphere. Obvious genetic changes took place as a result of chemical trauma on insects, plants, and so on.

Is there a difference of kind in this, in the recombinant situation?

We had supercockroaches, for example, that resist DDT, and other things of that sort.

Dr. FREDRICKSON. You can by many other techniques create so-called genetic pressures which drive organisms to develop modifications which allow them to survive. Clearly, mutagens—not only mutagens, but other chemical agents—can have this same effect.

Whenever you introduce a new antibiotic into the practice of medicine you're creating genetic pressures which will automatically favor certain organisms which have resistance to the antibiotic, for example.

Mr. BROWN. We've seen some hazards of that sort, as reflected in human beings, the thalidomide babies and other things of that sort.

Those kinds of babies don't normally occur in normal evolution, do they?

Dr. FREDRICKSON. Of course, there is a major difference in that tragic example, Mr. Brown, in that those babies will not reproduce offspring with the same injury because the injury did not result from induction of genetic changes, but changes during the stages of differentiation.

That may be why the use of recombinant DNA techniques have excited so much imagination—perhaps excessive bursts of it—in that presumably by changing the genes we may create new species which will reproduce and find new niches in the environment.

Mr. BROWN. Well, chemical agents can produce changes that will reproduce and will not reproduce genetically.

Dr. FREDRICKSON. That is true. But there you were inducing usually point mutations within the genetic substance of the animal itself, the single species. Here you can add strands of DNA which are entirely different genetic material and which may possibly be a much greater leap toward change in the nature of characteristics of that organism.

Mr. BROWN. Well, the thrust of my questioning, if we can go back to the general problem of chemical intervention in the biosphere, is whether or not, since you emphasize so much the hazards and safety aspects, there is a difference in kind between recombinant DNA research and the kind of research that led to the development and widespread application of chemicals to the biosphere. Many of these are causing cancer, many other kinds of diseases, distorting all kinds of vegetable and animal life, causing almost daily human deaths.

Mr. BROWN. And increases diversity, I presume?

Dr. FREDRICKSON. Yes. There is an opportunity to test the maximum limits of increasing diversity and perhaps to determine far better than we've ever understood before what controls that diversity, what are the limits to expression of unusual genetic combinations.

Mr. BROWN. Yet the guidelines, which have been developed, and the other concerns with regard to regulation, are not concerned in the slightest with the problem of either increasing or decreasing genetic diversity, but with safety in the laboratory. And that's the point that I'm reaching here.

Shouldn't we have a broader concern?

Dr. FREDRICKSON. Well, I think that we are at a first stage of that problem, in the sense that now that recombination is possible, it will be possible to learn enough about its capabilities to then open up that second debate, which you suggest. But we really don't know enough about the feasibility of using these techniques or the capability of creating diversity to any effective degree, and we can only learn that by the next step in the laboratory, and it is the purpose of the guidelines to take that next step safely, to confine any possible uncertainties or hypothetical hazards to the laboratory.

If it works, Mr. Brown, then I can see a need for great concern with the next stage.

Mr. Brown. There is sometimes dicussion in the Congress about what would have happened if 100 years ago we had concerned ourselves with the impact upon American culture of the development of the automobile, and whether we might have pursued a wiser course if we had analyzed the deaths, and the accidents, and the losses, and the changes in lifestyle, and all of the other things produced by the automobile, and the petroleum industry.

Now, concerned with regulating the safety of research in internal combustion engines 100 years ago since there weren't even many safety laws in those days—and we obviously weren't concerned with forecasting the impact of a new technology on society. But if we had, we might have done things differently

And I'm trying to get to a point today. We have new tools, we have technology assessment procedures for example. To your knowledge has any substantial effort been made to assess this technology in terms of its impact 50 years from now on either American society or the human race?

Dr. FREDRICKSON. In a limited way we've had some experience with technology assessment in the preparation of the draft environmental impact statement context of on the issuance of the NIH Guidelines.

It is extremely difficult to look forward a great distance in this area. It is quite possible that 5 years from now we might discover that there is so little opportunity or capacity for the expression of foreign genes in organisms that what we have been debating here was a paper tiger.

I think that we really cannot make a useful technology assessment beyond imagining various scenarios. Until we proceed far enough to have a glimpse of the true power of these techniques, beyond the capacity to reproduce apparently pure genes in large quantity, we do not have enough evidence to adequately assess this new technology.

Mr. BROWN. I know that it's a difficult question, but I'm sure there would be no difficulty in drawing up several scenarios that show the whole structure of human evolution change. It might be useful to

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.

Following the line of questioning suggested by Congressman Brown, it seems to me that in confronting the unknown, in dealing with the boundary between knowledge and ignorance, there is a real danger to make an assumption that we already know enough to say that we do not need to know any more.

I wonder if we do have enough knowledge in this field now to be able to say confidently that we do not need to know any more.

Dr. FREDRICKSON. No, Mr. Chairman. I think we do not. In fact, one sometmes hears a cry that we should have a moratorium until we get it all straightened out.

But, as a matter of fact, we shall never get it straightened out until we know more. In my view, it reminds me of a story about Kansas that was prevalent in the area of Colorado in which I grew up. The story goes that in the State of Kansas there was a law that said when two trains approach an intersection at the same time neither shall proceed until the other has gone on.

Chairman THORNTON. I'm familiar with that law. It was actually on the statute books.

Dr. FREDRICKSON. And in some ways that would be the nature of halting all search, all inquiry for more knowledge. I'm afraid that we cannot proceed until we have gone on, and I think it is the attempt of the NIH guidelines and of this move toward regulation to extend them to all aspects of the use of such techniques that represents an attempt to do this with prudence and with as much care—and perhaps more excessive regulation than is necessary—but nevertheless with the public interest in mind in both regard to safety and the possible use of this knowledge.

Mr. BROWN. Mr. Chairman.

Chairman THORNTON. Yes, Mr. Brown?

Mr. BROWN. Could I just ask one supplemental question?

Dr. Fredrickson, all of us on this Committee are supporters of science and friends of science. I don't think our main problems, from the standpoint of public policy, arise with the policing of science. But dangers may arise in that interface where science and industry or commerce get involved—with the chemical industry, for example—although there probably are some examples of where accidents occurred in the R. & D. that led to the development of pesticides, and so on—it isn't nearly as severe as the situation that exists in industry in the manufacture and production and use of recombinant DNA techniques.

Now, if we are to profit from the lessons of a generation of increasing dissemination of chemical pollutants, we should be concerned with the commercial use and production of whatever the products of recombinant DNA research are.

And I am wondering if we can visualize this problem clearly enough now to say that we need to set policy lines for the utilization of this technology, assuming that the R. & D. does bear fruit of some sort.

Mr. HOLLENBECK. Fine. You are to be commended for that approach, in my opinion.

Now, there has been some mention made of accidents and the possibility of accidents with regard to this research.

Has there been any feeling or any discussion in the scientific community with regard to establishing a strict liability standard, of liability of investigators, in the event of just such an accident?

Dr. FREDRICKSON. Yes; there has. There has been a good deal of discussion, discussion that we have held with scientists, and discussion within the Federal Interagency Committee, partly stimulated by S. 621, introduced by Senator Bumpers and the companion bill by Representative Ottinger.

It was the feeling of the Interagency Committee that the liability portion of the Bumpers-Ottinger bill posed a serious block to the furtherance of this research, because it would require all institutions to attempt to get heavy indemnity coverage, and if they failed to obtain it, they would have to cease all research of this kind, unless the Federal Government agreed to indemnify them.

It was the committee's feeling very strongly that liability should be left to State and to local laws.

Mr. HOLLENBECK. All right.

Thank you, Mr. Chairman.

Chairman THORNTON. Thank you, Mr. Hollenbeck.

I do want to pursue further the question of how effectively you solicit the input of the public into the decisionmaking process.

I believe you responded that the results of the decision were published. There has been concern expressed that the public is not involved in the formulation of the decisions which are announced, only that they are later advised. For example, I would like to ask whether a notice of workshops or hearings was published other than in the Federal Register, or is that publication the only publication which is made?

Dr. FREDRICKSON. I'll ask Dr. Gartland, with regard to the Recombinant Advisory Committee, how are those meetings published?

Dr. GARTLAND. At the present time they are announced in the Federal Register. We're giving serious consideration to a wider dissemination of announcement, perhaps through scientific and or public journals. But to date it's been basically the Federal Register.

Chairman THORNTON. I would submit that in view of the wide public interest in the subject that I'm pleased to hear you say that you are giving consideration to this.

Dr. FREDRICKSON. With respect to the February 1976 meeting of the Director's Advisory Committee that reviewed the guidelines in public forum, we went beyond the Federal Register announcement and specifically invited some 20 organizations that we knew had a heavy interest, particularly in the environmental area, to this meeting. We also invited a number of people whose persuasions we knew were widely different with respect to the guidelines.

Chairman THORNTON. Well, I just want to preface this question with the statement that there has been a great deal of concern expressed about whether the public is involved in the decisionmaking process.

I think it would be appropriate for you to be cognizant of this expression of concern. And I take it that you are saying that you are going to increase efforts to be sure that the public is involved.

chemistry and Chairman of the Committee on Genetic Experimentation (COGENE), recently established by the International Council of Scientific Unions. The primary focus of COGENE is on the recombinant DNA issue.

STATEMENT OF DR. WILLIAM J. WHELAN, CHAIRMAN, DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF MIAMI SCHOOL OF MEDICINE

Dr. WHELAN. Thank you, Mr. Chairman. Thank you for inviting me.

As you say, I'm a biochemist, but I am not myself engaged in research on recombinant DNA.

The reason that I became involved is because I am the Secretary General of the International Council of Scientific Unions, and the members of that Union, along with members of other scientific unions, have a keen interest in the new technology that you are discussing.

That led, in turn, to my becoming the chairman of this new Committee on Genetic Experimentation. It's so new that it has not met yet. It goes under the acronym of COGENE. And it's a scientific committee of the International Council of Scientific Unions, which we call ICSU.

It came into existence last October in Washington. The General Assembly of ICSU held its biennial meeting at the U.S. National Academy of Sciences, and COGENE came into being by the unanimous vote of the members of that assembly.

First, to tell what is ICSU. It is an international, nongovernmental scientific organization composed of 18 international scientific unions and 64 national members. Any nation with any pretension to organized science is a member of ICSU.

Each union represents a scientific discipline, such as chemistry. The national members are not governmental organizations, but are usually the supreme scientific organizations of the member country, in our case the U.S. National Academy. Since ICSU was created in 1931, it has adopted a policy of nondiscrimination, affirming the rights of all scientists throughout the world—without regard to race, religion, political philosophy, ethnic origin, citizenship, sex, or language—to join in international scientific activities.

The principal objective of ICSU is to encourage international scientific activity for the benefit of mankind, and it does this by initiating, designing, and coordinating international scientific research projects. It acts as a focus for the exchange of ideas, the communication of scientific information, and the development of standards.

The committees or commissions of ICSU are created to organize programs in multi- or transdisciplinary fields which are not completely under the aegis of one of the member scientific unions. A typical and topical example is the Committee on Space Research, which brings together 11 of the scientific unions ad 34 national members.

It was natural, therefore, that ICSU, taking note of the potentially enormous significance to mankind of the newly developed science of recombinant DNA technology, should move to establish a scientific committee to work in this area. As a relative latecomer to the scene, ICSU gave regard to the fact that if this field of research suffers from anything it is not from lack of committees to examine it.

formed during the recent discussions of recombinant DNA held at the U.S. National Academy about 3 weeks ago.

That Academy forum served as a most adequate exposé of the concerns coming from all corners of society. We heard of the problems of regulating the research itself, the forbidden experiments, the safety measures, the potential hazards to researchers and to society in general, the moral and ethical concerns, with the fears that industry would carry out dangerous experiments behind closed doors and the concern—or even outrage—that new forms of life, potentially the harbingers of doomsday, would be brought into being to fatten corporate profits.

But something seemed to me to be lacking from that debate. It was entirely understandable that the citizens of Cambridge, Mass., should view with alarm the prospects of dangerous organisms escaping from the Harvard laboratories. It was equally understandable that many of those present and the citizens of Cambridge wished such research to be moved elsewhere than their city, that others should call for the research to be confined to a few key installations or, at the extreme, to be banned outright.

But I heard very little by way of concern at what might be happening outside of the United States. The arguments revolved almost wholly around the domestic scene.

Recombinant DNA technology has been likened in its potential impact to the discovery of nuclear fission. But it has taken 30 years for nuclear fission to come within the capability of the enterprising graduate studnt or the terrorists. By contrast, recombinant DNA experiments can already be carried out almost anywhere, using freely available methodology and with relatively simple facilities. The experiments that are still banned in the NIH guidelines can be conducted readily by anyone lacking respect for the ban or who is ignorant of the need for the ban.

Plagues and scourges caused by pathogenic microorganisms have no respect for persons or the boundaries of cities, States, or nations. If the potenial hazards are real hazards, little would be achieved if the research became outlawed only in the United States. It might be going on in Canada, or Mexico, or Albania, and if the research really is dangerous, that would be just as hazardous to the citizens of the United States as if it were carried out at Harvard.

As already alluded to by Dr. Fredrickson, there is a clear and pressing need for action on the international scene. The concerns of the researchers are not national concerns, the applicability and the enforcement of guidelines is not merely a matter of securing observance throughout the United States, the problems of industry are not national, nor are the concerns of the lay public or the social issues. All of them are international problems calling for international agreement and regulation.

I do not presently see much by way of collective activity at the international level—and this is certainly not to contradict the remarks that Dr. Fredrickson made, because the contacts are certainly there. But I'm referring to organized activity which has a basis for continuity, and because of this the kinds of things that this committee might do may seem, in their totality, to be overambitious. But they simply represent the collection of the things we think ought to be done on the

form the face of society. I don't think it needs a crash program. I think it needs a long, careful examination.

The United States has already rendered signal service on the world scene by the actions of the National Institutes of Health in producing the safety guidelines and the environmental impact statement, a statement and guidelines that have universal applicability. I hope the United States will continue its examination of the many other issues also involved, such as patents.

But I hope it will also take the lead in calling for universal respect and concern for the impact of this new technology on society, for safety measures, for the protection of the environment, and for common international sanctions on any misuse of the technology.

My impression at the moment—and it was formed after the National Academy debate—is that I'm afraid that the divisiveness one sees in debates in the United States, and the apparent concentration on problems as if they were only internal problems are causing people to lose sight of the larger issue; namely, international initiatives are needed.

I hope that the United States will help to promote international cooperation in this research, and make the basic and applied knowledge freely available so that when the potential, and one has to admit still conjectural, benefits of the research become available, they become available to all.

Thank you.

Chairman THORNTON. Thank you very much for your very excellent testimony. We will include the attachments to your testimony in the printed record.

[The material follows:]

REPORT OF THE *AD HOC* COMMITTEE ON RECOMBINANT DNA MOLECULES

The *ad hoc* Committee on Recombinant DNA Molecules, charged by the General Committee with reporting on the implications and potential of research on recombinant DNA,

recommends that a Scientific Committee be established to monitor, assist and report on research in this branch of molecular biology. The ad hoc *Committee offers its report in the form of a preamble, a proposed constitution of the Scientific Committee, a suggested annual budget, plus the minutes of the* ad hoc *Committee meeting and annexes of papers read into the record of the meeting.*

PREAMBLE

In a presentation to an Advisory Committee to the Director of the U.S. National Institutes of Health on 9 February 1976, Paul Berg stated that:

"The past 25 years have witnessed a revolution in our understanding of the structure and workings of the genetic machinery of living cells. Although the theoretical implications of this understanding were apparent to biologists and chemists from the beginning, the possible practical benefits of this knowledge to medicine, agriculture and industry have become clearer only recently.

One potential benefit that captured the imagination of scientists and laymen alike was the notion of 'genetic engineering' - the directed modification, or even construction, of new kinds of genetic constitutions for animals, plants and eventually man. But partly because of the exaggerated and of the misleading claims of the popular press, and of scientists and laymen as well, the words genetic engineering evoke concern as well as excitement."

The excitement stems from the possibilities of being able to analyse the molecular basis of gene expression and heredity in higher organisms and eventually to create new organisms with desired genetic characters.

The possibilities now open to the experimenter arise from three advances in technology, namely the ability (i) to cleave the hereditary material of the cell (DNA) at specific points, yielding fragments that control the synthesis of particular functions of the cell, (ii) to rejoin mixtures of such fragments from different organisms so that packages of genetic material containing functions derived from the two species are obtained and (iii) to introduce such semisynthetic genetic material into a cell so that the DNA can multiply, as the cells multiply. The cells thereby carry out new synthetic

(i) the importance of research on recombinant DNA molecules;

(ii) the need for such research to proceed under appropriate safeguards;

(iii) recommendations on safety measures and specifications for containment facilities;

(iv) technical details concerning the availability and choice of organisms and materials.

(c) subject to the foregoing safeguards, to encourage the universal availability of suitable strains.

(d) to foster international scientific exchange by acting as a link between other committees and correspondents, by personal visits, training courses, symposia and workshops.

(e) other objectives as may be recommended.

This *ad hoc* Committee met on 1-2 July 1976 in Heidelberg.The Committee is unanimous in recommending to the General Committee and General Assembly of ICSU that a Scientific Committee on Recombinant DNA Research (SCORD) should be established. The work of such a Committee would be of major interest to several of the Unions federated in ICSU, the subject is of the highest scientific importance and demands the formation of a strong Committee. The importance of research on recombinant DNA will only grow with time and will develop ramifications of certain significance to science and society. In every respect the subject fulfills the criteria laid down in Article 16 of the ICSU Rules for Scientific and Special Committees which reads as follows:

16) The following criteria should be satisfied if a Scientific Committee is to be created:

1. The work of the Scientific Committee is of major interest to not less than three Scientific Unions.

2. The task of the Scientific Committee requires the formation of a strong Committee to carry out the said task.

3. The programme of the said task is of a long-term nature.

When the programme involved is of limited duration, and only the first two criteria above are satisfied, a Special Committee should be formed for the task.

The *ad hoc* Committee drafted a proposed constitution for the Scientific Committee, together with a statement of membership, aims and purposes, and a suggested budget. These documents are attached. It is the unanimous recommendation of the *ad hoc* Committee that the General Committee and General Assembly of ICSU create a Scientific Committee and take steps to provide the appropriate financial support. The *ad hoc* Committee believes that it has fulfilled its mission and should now be disbanded.

W.J. Whelan, Chairman

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to achieve appropriate geographical representation and liason with other bodies active in the field.

SCORD may appoint Sectional Committees and Working Groups to assist in discharging its tasks.

III. FUNCTIONS

To accomplish the stated purposes and objectives The Committee shall direct its attention to the following tasks:

1. *POLICY CONSIDERATIONS*

(a) To observe governmental actions and to foster the development of informed public opinion in relation to research on recombinant DNA.

(b) To assist in establishing and harmonising national guidelines in order to facilitate international cooperation in research in this field and to ensure appropriate safety measures.

(c) To provide through its member unions and associated bodies expert advice on policy matters.

(d) To cooperate closely with other international organisations in order to reach all scientific disciplines concerned and to be available to all legislative and executive bodies.

2. *INFORMATION SERVICES*

As far as it is practical and useful, to collect and distribute the following information about research on recombinant DNA molecules:

(a) *Beneficial applications*

The benefits of research on recombinant DNA molecules have so far been entirely in the realm of pure science. It is believed, however, that this research can be applied in medicine, agriculture and industry to the benefit of society. Any such applications should be made known, to facilitate their use and to inform the public.

3. *TECHNICAL SERVICES*

(a) Subject to appropriate safeguards, The Committee should encourage the universal availability of suitable host and vector systems, perhaps by supporting a few centralized collections, or providing help on a less centralized basis to those prepared to maintain and distribute strains.

(b) It is in the interests of both safety and economy to reduce, as far as possible, the repetition of certain types of cloning experiment. The Committee may help by supporting at one appropriate centre the construction and maintenance of large populations of cloned segments of, for example, mouse or human DNA. Interested scientists could then go to that laboratory and select clones for their own work.

4. *TRAINING AND EDUCATION*

In the long-term interests of safety and science it is imperative that all scientists embarking on recombinant DNA research should be conversant with the practical application of safety guidelines and advanced experimental techniques. Therefore The Committee should promote the training of biologists in the techniques of recombinant DNA research. These opportunities should be created for those who do not, at the national or regional level, have access to training programmes.
These programmes might include (1) practical courses, (2) fellowships, (3) workshops, and (4) lecture tours.

IV. BUDGET

The *annual budget* required for the optimal accomplishment of the recommended tasks of The Committee is as follows:

Annual meeting of The Committee

If there are six members appointed by the General Assembly the cost of attendance is estimated as: $ 6,000

Liaison with other similar committees

It is envisaged that members of The Committee, or experts designated by The Committee, would attend meetings of other similar committees in order to provide proper coordination. Three such visits per annum would cost: $ 3,000

Minutes of the Meeting of the *ad hoc* Committee on Recombinant DNA Molecules

Heidelberg, 1-2 July 1976

The Chairman, W.J. Whelan, welcomed the participants.

J.C. Kendrew explained that during a discussion with P. Berg, prior to the Asilomar Conference on recombinant DNA, a suggestion had been made that the importance of the subject warranted the creation of an international non-governmental group of professional scientists which would include in its brief the questions of harmonization of guidelines and information exchange. This had been put to the Executive Board of ICSU which had convened a small group to discuss the question in Schloss Laxenburg in September 1975. The report of this group, which included a proposal for the creation of the present *ad hoc* Committee, had been accepted by the ICSU General Committee at its meeting in September 1975. The present group had been asked to submit a report to the ICSU General Assembly, which would be meeting in October 1976. The report should include a recommendation on the future role of ICSU in this area and, if it was agreed that ICSU should create a standing committee or commission, draft terms of reference should be proposed.

The WHO has a sub-committee on Safety in the Handling of Microorganisms and Cells employed in Research, but this covers a much wider field and is a governmental body.

M. Singer explained that a group of scientists at the 1973 Gordon Conference on Nucleic Acids had expressed concern about the hazards of some experiments that could be carried out by the new recombinant DNA technology. This concern had been transmitted to the U.S. National Academy of Sciences and the Berg Committee had been formed.

E. Wollman drew attention to the parallel situation in the 1930's in the early days of the development of nuclear physics and to the fact that there had been a lack of concern then about what might happen if the knowledge gained was misused. He explained that the International Association of Microbiological Societies' *ad hoc* Committee on Genetic Engineering had discussed the questions of hazards and misuses and had indicated its readiness to prepare guidelines. He asked if ICSU had a role to play in this field.

J.C. Kendrew said that ICSU had not yet decided to play a role: it had asked the present group for its advice on this subject. He personally felt that there is a need for an international group.

The Chairman suggested that an international group could play an important role in providing information to the general public, to governments and other decision makers, it would provide expert testimony, suggest an international code of practice, guidelines, carry out surveys of the laboratories doing work on recombinant DNA, help scientists by arranging training courses, bibliographies, lists of techniques, etc. He suggested that ICSU had a role to play particularly in relation to developing countries.

J.C. Kendrew gave a review of ICSU and of its activities. F.G.W. Baker provided information on the ICSU committee structures, composition and activities.

Japan

Y. Tazima explained that the Science Council of Japan had set up a Sub-committee on Plasmid Problems which includes scientists from various biological sciences (see Annex 3). An attempt had been made to try to obtain a consensus of Japanese research workers with regard to research on recombinant DNA. There was general agreement with the appeal made by the Berg Committee. The sub-committee had organized two symposia, its first on Plasmid Engineering, the second on Safety in Genetic Engineering. The latter had included a session on Inactivation of DNA, which seemed to be a serious problem but comparatively simple to resolve.

He said that he thought an ICSU Committee could serve a useful purpose.

United Kingdom

K. Murray drew attention to the summary in the paper prepared by J. Tooze for the Miles Symposium in June 1976 (Annex 1). He explained that the Ashby Report had proposed a series of measures that had gained acceptance. The Williams' working party had contacted a wide range of interested people and its report will be published shortly. The various Research Councils had been asked not to sponsor work which presented potentially serious hazards.
It was expected that the report of the Williams committee would recommend the establishment of a Central Committee which would consider proposals for research and the techniques to be used. It was expected that there would not be a rigid set of guidelines, but there would be recommendations on various categories of containment facilities. There would be local safety officers who could perhaps stop research pending further inquiries. He drew attention to the facilities offered to universities at Porton. These might be available to scientists from outside the U.K.

Industrial work in the U.K. was to some extent being overviewed by the Confederation of British Industry.

U.S.A.

R. Curtiss submitted a report on the activites of the NIH Recombinant DNA Molecule Program Advisory Committee (Annex 4). He explained that the Committee had made its final changes in the proposed NIH guidelines on 2 April 1976 and transmitted the revised guidelines to the Director of NIH who subsequently made some further changes. The guidelines commenced to be distributed on 23 June. Copies were distributed to members of the *ad hoc* committee.

Nucleic Acid Recombinant Scientific Memoranda (NARSM): This is a publication from NIH designed for rapid dissemination of information on recombinant DNA research. NARSM will be sent to any individual or group who requests to be put on the mailing list. If the number of reports submitted for inclusion increases, it will probably be issued monthly instead of quarterly.

EK2 (Safer Host/Vector Systems): Expert subcommittees of the NIH Recombinant DNA Molecule Program Advisory Committee have been established to make recommendations on certification of proposed EK2 host/vector systems. Five contracts had been awarded for design and preparation of certain host/vector systems and other contracts were proposed for testing such systems. Laboratories outside of the U.S. could submit proposals for these.

Courses: Two courses are to be held in September on biohazard containment control.

He felt that it would be useful if ICSU became involved, to act as an international focus for the consideration and development of guidelines. He suggested

that the conditions required are actually met. Work published on recombinant DNA experiments must indicate that it has had the approval of the commission. He drew attention to the fact that the academic community had insisted that the same rules should apply to eventual industrial or military research in the field.

2. The Brenner Concept

K. Murray drew attention to the concept of cloning a total digest of mouse or human DNA. This could be carried out at Porton and anyone interested would obtain the material they required. He suggested that such a facility should exist at the international level and wondered if the EMBL might provide it. To do such cloning a central point would minimize the number of times a potentially risky experiment had to be carried out.

3. Creation of a Committee on Recombinant DNA

W.J. Whelan drew attention to the terms of reference of the *ad hoc* Committee which includes the need to prepare a recommendation on the future role of ICSU, if any, and suggestions on the Terms of Reference of a continuing body, if it is recommended that one be created.

E. Reich proposed that ICSU set up a committee with terms of reference based on those of the *ad hoc* Committee. This was seconded by H.G. Zachau and adopted unanimously.

4. Draft Terms of Reference of the Proposed Scientific Committee

The Committee adopted the proposed terms of reference given in the attached report from the Committee.

5. Budget

The Committee suggested that a sum of about $170,000 would be required to carry out all the tasks foreseen (see report to President Brown).

It was felt that one of the first priorities should be in training and education, but that ICSU should endeavour to obtain funding for all parts of the programme.

6. Any other business

The Committee agreed that a second meeting was not required.

The Chairman thanked the members of the Committee for their work and J.C. Kendrew and J. Tooze for making the local arrangements.

The meeting concluded at 13.40 on 2 July.

The Committee on Genetic Experimentation

A SCIENTIFIC COMMITTEE OF THE INTERNATIONAL COUNCIL OF SCIENTIFIC UNIONS

FROM THE CHAIRMAN: Dr. W. J. Whelan Biochemistry—UMED P.O. Box 520875 Miami, Florida 33152 U.S.A.
Phone: 305-547-6265 Cable: Bioquimica Miami Telex: 519308

The International Council of Scientific Unions has created a scientific committee on genetic experimentation (COGENE), with the following objectives:

a) To serve as a non-governmental, interdisciplinary and international council of scientists and as a non-governmental source of advice for the benefit of governments, governmental agencies, scientific groups and individuals, in respect of researnh on genetic experimentation, the practical benefits that may be derived therefrom and the need for such reaearch to proceed under appropriate and generally agreed safeguards;

b) to assemble, review and generally make available information on safeguards, containment facilities and other technical matters;

c) to foster opportunities for the training of and international scientific exchange between workers in the field;

d) to make itself available as a medium through which the many national, regional and other international bodies with intereats in recombinant DNA molecules may communicate;

e) to take note of the widespread concern over the possible deliberate or inadvertent dispersal of agents constructed by recombinant DNA techniques, to be vigilant regarding such possibilities and to attempt to foster public discussion of these situations should they arise.

The committee is composed of persons appointed by ICSU, and by seven of the member unions of ICSU (Biochemistry, Biological Sciences, Pure and Applied Chemistry, Immunology, Nutrition, Pharmacology and Pure & Applied Biophysics). FAO, UNESCO and WHO have appointed observers.

The members are: A.A. Bayev, (U.S.S.R.), P. Berg (U.S.A.), G. Bernardi (France), S.N. Cohen (U.S.A.), H.N. Munro (U.S.A.), K. Murray (U.K.), N.K. Notani (India), E. Reich (U.S.A.), R. Riley (U.K.), C. Steinberg (Switzerland), J. Tooze (B.R.D.), I. Watanabe (Japan), W.J. Whelan (U.S.A.) and E. Wollman (France). The observers are A. Bozzini (FAO), S. Passman (UNESCO) and V. Sgaramella (WHO).

The chairman is W.J. Whelan and the secretary is Dr. J. Tooze (E.M.B.O., Postfach 102240, 69 Heidelberg 1, Federal Republic of Germany).

The first meeting of COGENE will be held in Paris in May.

March 1977

WJW:mc

I think one has to begin by making the guidelines applicable all around, because at the moment you don't apparently have any mechanism for controlling research outside the laboratories funded by the National Institutes of Health. That would be a beginning.

But after that, try to be helpful to what it is that industry needs, but neither pander nor be expedient in giving in to pressures from industry, nor should one hastily pass legislation which may be too restrictive. I'm asking for steering the middle course.

This technology is going to be with us for the rest of time. It might even be argued that until there area real benefits to be seen, one should not allow industry to go ahead full steam. There could be a good argument for asking them to delay, to wait until there has been a careful examination.

Mr. BROWN. Well, I would say, if prior experience is any indication, that if we enact regulations on private industry, it will cause some delay. I don't know whether that's necessarily good or not, but it probably will happen.

I'm not really so much concerned with the regulation of the research, but I do welcome your view which is only reasonable, that all of this research in whatever sector should be subject to a common framework of legislation. But I am more concerned about the situation when we move from the research to the development and commercialization stage, which I think is going to pose policy questions much more serious. I would like to see us avoid those in a much better way than we did in connection with the toxic chemicals situation.

We have just gotten to the point this last year of enacting comprehensive law with regard to the toxic chemicals, after a long struggle, and after the industry has invested billions. The impact of that investment has had major impacts upon this country and the world. That's the sort of thing I would like to do a little better job of, if this area of research has the developmental potential that the chemical industry did.

Dr. WHELAN. As a comment, I would like to say that I don't believe the problems that industry sees are being articulated in an organized fashion, and this is why we would hope ourselves to bring people together and ask them what their problems are so that they can be openly stated. It's certainly a very difficult situation, because there are concerns within industry that some competitors may get ahead of the other, that in one country they may decide to take risks in the hope of getting patents.

I was extremely disappointed to see a charge leveled that some of the people who called for the moratorium did so in order that they could get one jump ahead by patenting some of the results. When the debate descends to that level, it's extremely disappointing.

Chairman THORNTON. Thank you, Mr. Brown.

Mr. Hollenbeck?

Mr. HOLLENBECK. I'll pass, Mr. Chairman.

Chairman THORNTON. I would like to ask a couple of questions.

With regard to your prepared testimony, you mentioned the need to conduct risk-testing experiments designed to examine the reality of alleged or real hazards. You state that you're in touch with organizations which are planning such experiments, and you have your own panel of experts now planning experimental protocols.

common voice. The loudest voice is probably coming from the Pharmaceutical Manufacturers Association, which has said publicly at a number of hearings that they feel the NIH guidelines should be and will be adopted by their member companies, with what they term "minor modifications which will have no effect on safety." That is about the firmest position I have heard. And I haven't heard them change that position.

Dr. TALBOT. If I may speak.

Chairman THORNTON. Yes, Dr. Talbot.

Dr. TALBOT. I've heard George Wald mention this before and cite a news article, which I believe appeared in the Washington Post, a report of a meeting held at the Department of Commerce with representatives from industry, which stated that industry had shifted its position.

But I've spoken to other people who were at that meeting and who didn't hear it that way. I believe it's an erroneous report in the press, stating that industry did shift its position. Other people at that meeting have relayed to me that what they heard industry say at that meeting was not a shift in its position.

Chairman THORNTON. In any event, what you're saying that it's a matter of discussion or debate as to whether it was a shift in position or merely a restatement of position.

Is that correct?

Dr. TALBOT. The newspaper article gives the impression there was a shift in position, but other people I've spoken to who were present at the meeting say what they heard did not lead them to believe there was a shift in position.

Chairman THORNTON. Thank you very much.

We have discussed previously today the distinctions between recombinant DNA research and other forms of genetic engineering, and the difficulty in drawing a line between these types of research.

If the United States, absent a world agreement to do so, were to unilaterally ban further experimentation in recombinant DNA research, can you address the question of what effect this would have on our role in science, in basic biology, with regard to science in the rest of the world?

Dr. WHELAN. I could answer that from two points of view.

The first is that there is no question I think that very important basic knowledge is certain to be gained from this research. It would be a pity if the resources of American biologists—and, after all, the technology began here—were frustrated in their attempts to pursue those ends.

As regards the second question, that if the potential benefits become reality—and they're still potential—I don't see how the United States could hold off participating. I don't think it's realistic to consider that the research could be stopped here.

Chairman THORNTON. Do you perceive a possible distinction and perhaps containment—if I may use that expression—of research efforts by permitting research activities to go forward, but not the production or dissemination of any of the results of that research—that is, not the release of products?

Dr. WHELAN. It's very difficult to answer that question. I think one could only move ahead on the basis of experimentation. Certainly, one

it may be an omission of a gene, or a failure of a stop/start mechanism to work properly?

Am I in the ball park with my understanding?

Dr. TALBOT. Most natural mutations involve either a change in the DNA or a deletion of DNA, and don't involve additions of DNA, as in this case. We are adding the extra fish DNA.

Dr. WHELAN. But we're really talking here about adding something that E. coli never had before, so the normal kind of change that one talks about, mutations, wouldn't bring about the effects that the recombinant DNA methodology would.

Chairman THORNTON. You are changing a property of the organism, I suppose; or you're changing its genetic information, so that it does carry that property forward?

Dr. WHELAN. Yes, such as endowing it with the capacity to synthesize insulin, which we don't think it presently has, and we add that to the capability of the bacterium, and that represents a difference from the normal type of mutation that may delete or release a capacity that the organism has.

Chairman THORNTON. May I inquire whether you would be willing to respond to such written questions as may be addressed to you following the hearing?

Dr. WHELAN. Indeed. I'd be very happy to.

Mr. BROWN. Mr. Chairman, while you're cogitating, could I pursue a question or two?

Chairman THORNTON. Please. Go right ahead.

Mr. BROWN. You have mentioned the possibility of commercial exploitation of a bacteria's capability to synthesize insulin.

Is this something that could conceivably be imminent, that is, within a period of 5 years?

Dr. WHELAN. It's already been claimed last November by scientists at the University of Minnesota. But I've seen no followup to this. They claim they had put the human gene for insulin synthesis into yeast, and the rather brief account of this went on to say that no disclosure of how they did it was being made because they were seeking worldwide patents.

I heard no more about it, and I wonder if any of my colleagues have. This was in Science News last November.

Dr. GARTLAND. No.

Dr. WHELAN. I think it's surprising that it allegedly happened so soon.

Mr. BROWN. You see, this does raise the question of the immimence of the need for not only safety regulation of research and development, which is essentially under the guidelines and is what they purport to do; but also raises the question of policy with regard to the permitting of commercial production involving this kind of a process.

Now, can we separate the genetically altered bacteria, which we'll say can synthesize insulin, from the product insulin? Is that insulin such that if it goes in to normal market channels, there is none of this recombinant DNA that could be a part of that insulin? I ask the question out of pure ignorance.

Dr. TALBOT. I would assume the company having this bacteria would isolate the insulin from the bacteria and attempt to sell the pure insulin free of all recombinant DNA materials. This would be subject to the

years—the tremendous possibilities in the use of micro-organisms for new products, either for food protein, but particularly for enzymes.

An example is a new technology in which the United States is leading at the moment, one that happens to be causing trouble in the sugar industry in Hawaii, because Iowa corn is being used to produce at lower cost a product which is identical with a sweetening agent normally made from sugar. And it's a large operation—6 billion pounds a year—that uses beautifully sophisticated enzyme technology.

One could see very clearly how enzyme technology could be improved still further by recombinant DNA techniques. And it wouldn't involve the release of the recombinant DNA molecules.

Mr. BROWN. But another very common example is some sort of a recombinant bacteria which eats oil, for purposes of oil spills. Take that as an example. Obviously, to accomplish cleaning up the goal of cleaning up the oil that's spilled on a waterway, we have to release the bacteria, which introduces into the biosphere a very large quantity of strains that perhaps have never existed before.

And I get back to the question: Do we have techniques for ascertaining the environmental impact of this kind of a situation? Have we sought to explore this problem in detail?

Dr. WHELAN. I believe the techniques are there, but the testing would be a long and lengthy process. Certainly any of these new creatures would have to be subject to exceedingly thorough testing. I appreciate very much the concerns of the people who are apprehensive about turning these things loose.

I don't think they should be until there's been an exceedingly thorough examination.

Mr. BROWN. I can imagine the problem that would exist if we had to worry about one of these new strains of bacteria and its interaction with every other strain of bacteria to which it might be exposed, and what the possible genetic development might be down several hundreds of generations. It might be an unsolvable problem.

I'm just trying to visualize what it would be.

Chairman THORNTON. Thank you very much, Mr. Brown.

Mr. Hollenbeck, do you have any questions?

Mr. HOLLENBECK. No.

Chairman THORNTON. We do have a vote signaled on the floor of the House.

At this time I want to express appreciation on behalf of the subcommittee to each of the witnesses this morning.

Dr. Whelan, your testimony and your responses were very fine.

We will schedule further hearings on this subject, to be announced at a later time. This hearing is adjourned.

[The hearing was adjourned at 11:35 a.m, to reconvene at the call of the Chair.]

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

WEDNESDAY, APRIL 27, 1977

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

The subcommittee met, pursuant to notice, at 10:14 a.m., in room 2318, Rayburn House Office Building, Hon. Ray Thornton (chairman of the subcommittee), presiding.

Mr. THORNTON. Good morning. Today we resume consideration of science policy implications of DNA recombinant molecule research. We began hearings on this subject March 29, 30, and 31 and during those hearings received testimony from a number of distinguished scientists on the basic biology of this research, on the potential risks and benefits of this research and on actions being taken so far by the Federal Government and the governments of other nations to regulate the research. Those hearings provide us with a good bit of background information which we felt we needed before considering the broader science policy questions that are of major concern to this committee. Today we are going to explore further some of the concepts touched upon in our earlier hearings, particularly those scientific facts from evolution and epidemiology which are relevant to the DNA recombinant molecule issue.

The subcommittee believes that these aspects of the issue deserve fuller public discussion. Some people have suggested that DNA recombinant molecule research is tampering with evolution or that it is creating new DNA sequences which have never before occurred in nature.

Two of our witnesses this morning are engaged in basic biological research which is central to these issues and it is at the forefront of research in this field. We would especially like those witnesses to address the the potential for natural recombinant DNA and the concept of evolution at the molecular level.

Some people have also suggested that risks of new, unknown, and unpredictable diseases are too great to permit DNA recombinant molecule research to continue except under the strictest containment measures or perhaps even not to continue at all.

We have two witnesses knowledgeable in the field of epidemiology, the science which deals with the incidence, distribution, and control of disease. We have asked them to address this argument by presenting to us those facts which might be related to the potential spread of some

A SPECULATION ON THE ORIGIN OF PROTEIN SYNTHESIS*

F. H. C. CRICK, S. BRENNER, A. KLUG, and G. PIECZENIK **
Medical Research Council, Laboratory of Molecular Biology, Hills Road, Cambridge, England

Abstract. It is suggested that protein synthesis may have begun without even a primitive ribosome if the primitive tRNA could take up two configurations and could bind to the messenger RNA with five base-pairs instead of the present three. This idea would impose base sequence restriction on the early messages and on the early genetic code such that the first four amino acids coded were glycine, serine, aspartic acid and aspargine. A possible mechanism is suggested for the polymerization of the early message.

1. A Speculation on the Origin of Protein Synthesis

The origin of protein synthesis is a notoriously difficult problem. We do not mean by this the formation of *random* polypeptides but the origin of the synthesis of polypeptides directed, however crudely, by a nucleic acid template and of such a nature that it could evolve by steps into the present genetic code, the expression of which now requires the elaborate machinery of activating enzymes, transfer RNAs, ribosomes, factors, etc.

One solution is that the original mechanism was made mainly if not entirely of nucleic acid so that to express the earliest version of the genetic code (which was probably at that time both partial and rather inaccurate) little or no protein was required. It was suggested by Smithies (quoted in Crick, 1968) that in the beginning no activating enzymes were necessary because each primitive tRNA had a special cavity to hold its own amino acid. Woese (1967) made a similar suggestion. We shall not concern ourselves with this aspect of the problem here. It has also been suggested that the original ribosome was made entirely, or almost entirely, of nucleic acid. The hope has been that when the three-dimensional structure of the nucleic acid in the two portions of the present day ribosomes becomes known it may be possible to guess the structure of the primitive ribosome. For example the first ribosome may have consisted only of the ancestor of the present 5S RNA.

2. Protein Synthesis without Ribosomes

Here we consider an even more drastic simplification. We shall assume that originally no ribosome at all was necessary and that the ordering of amino acids in protein synthesis was accomplished using only messenger RNA and a few primitive tRNAs. This possibility has already been mentioned by Woese (1967 and 1972). The justification for this approach is that the synthesis of the basic clover-leaf structure of tRNA is not, on reasonable hypotheses, as improbable as might at first sight appear. This argument, first published by Orgel (1968) has

* This paper is dedicated to the memory of Dr. Aharon Katzir.
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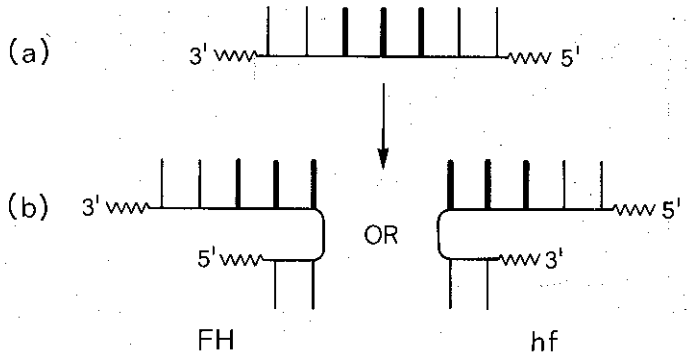

Fig. 1. The two configurations postulated for the anticodon loop, shown symbolically. (a) The seven bases of the anticodon loop drawn in a straight line. (b) The configuration proposed by Fuller and Hodgson (FH) is shown on the left. The other, the hf configuration suggested by Woese, is on the right. Each vertical line represents a base. The thick lines show the three bases of the present anticodon.

the second (labelled by Woese the hf configuration) the five bases at the 5′ end form a stack (see Figure 1). The possibility of such a transition playing an important part in protein synthesis was first put forward by Woese in the ingenious paper quoted above. He also (Woese, 1972) suggested it might play a part in the primitive environment.

(3) We assume, following Woese, that when an amino acid is attached to a tRNA molecule the latter takes up the hf configuration; when a peptide is attached the configuration flips to FH. When neither is attached we make no special prediction – possibly both configurations can exist in equilibrium.

There is a fourth postulate which, if not absolutely necessary, makes the important conformation energetically more favourable and thus several undesired arrangements less favourable. This assumes that there is a weak unspecific interaction between two tRNA molecules which are adjacent on the messenger RNA, the first being in the FH configuration and the second in the hf one.

5. The Suggested Mechanism

With these four assumptions the outlines of the mechanism are obvious. Consider first the state in the middle of the synthesis of a polypeptide chain when the tRNA (in the FH configuration) is held to the mRNA by five base pairs (the bases in the anticodon loop being unmodified) as shown in Figure 2A. The tRNA bearing the next amino acid coded for then enters the adjacent position, in the hf configuration, also making five base pairs, as in Figure 2B. Then, by proximity, probably aided by a general non-specific catalyst, the polypeptide chain is transferred to the new amino acid in the usual way, resulting in Figure 2C. This causes the tRNA which now has the polypeptide attached to flip to the HF configuration (Figure 2D) thus causing the previous tRNA to be held by only three base pairs, so that after an interval it falls off the mRNA. The process then repeats.

The primitive code, on this theory, was therefore a partially overlapping quintuplet code, the number five arising because a loop of seven bases (which we take as given) can have a stack of five bases on one side and two on the other, so that $5 = 7 - 2$. The movement along the mRNA of three bases at a time is produced because of the flip mechanism, since $3 = 5 - 2$.

It is almost essential, as has been emphasized before (Crick, 1968) for the primitive system to have moved along three bases at a time (rather than, say, two bases at a time) because of the principle of continuity. The fact that a sequence of five adjacent bases must be recognised places important restrictions on the base sequences of the early messages and of the primitive anticodons.

6. Possible Primitive Genetic Codes

We must now consider the implication of these ideas for the primitive genetic code. Here a fair number of possibilities exist. We shall only illustrate a few rather simple and indeed over-simplified possibilities.

We shall tentatively assume that the restrictions on the (unmodified) base sequences found in the present anticodon loops (Barell and Clark, 1974), are relics from the primitive tRNAs. These restrictions can be written

$$3' \quad \mathrm{NR}\alpha\beta\gamma\mathrm{UY}$$

(where the anticodon sequence is written backwards, with the 3′ on the left) using the usual notation (and ignoring modified bases).

N = any of the four bases, A, G, U, or C

R = a purine, A or G

Y = a pyrimidine, U or C

and where the α, β, γ stand for the three bases of the present anticodon, the third (or wobble) position (γ) being on the right.

To simplify discussion we now assume that some degree of "wobble" (that is, U = G pairing) was possible in *all* positions and also that in the primitive tRNA the Y at the 5′ end of the loop was a U (and not a C). Thus our primitive family of anticodon loops can be written

$$3' \quad \mathrm{NR}\alpha\beta\gamma\mathrm{UU}.$$

We now need to put restrictions on the messenger sequence so that five base pairs (normal or wobble) are always possible on both the FH and hf configurations of the tRNA. (The constraint arises because the bases adjacent to the anticodon must also pair with the message). Thus for the message we deduce the repeating family of sequences

$$\ldots\ldots, \mathrm{RRY}, \mathrm{RRY}, \mathrm{RRY}, \ldots,$$

(where the commas are written to show the correct phase of reading) and for the anticodon the family

$$3' \quad \mathrm{UGYYRUU}$$

If we are prepared to relax the rule that there must always be five good base pairs in both the FH and the hf configurations then we can use for the anticodon loops the family

3′ UG*NYR*(U)U

which corresponds to the set of codons N_{GC}^{AU}, at the cost of occasional U = C and U = U pairs (which may be possible but rather weak (Crick, 1966)) in the position marked with a bracket. In the present code this adds the amino acids tyrosine, cysteine, histidine and arginine. A less likely alternative is the family

3′ (U)G*YNR*UU

which corresponds to the codon set ${}_{G}^{A}N_{C}^{U}$. The additional amino acids for these codons are at present isoleucine, threonine, valine and alanine. Both of these codon sets, separately, are comma-free. The second set is less attractive in that the possible weaker base pairing occurs not only in the hf configuration but also in the FH configuration. This latter is the configuration needed to hold the growing polypeptide chain to the mRNA and one might expect it to be the most stable of all. Note however that these codons might have included GC_{C}^{U} which now codes for alanine, another likely candidate for a primitive amino acid and that, since three G ≡ C base pairs would give extra stability, the use of the codon GCC, combined with the four mentioned previously, is not unattractive. Whatever the details, the point is that new anticodons can be introduced by relaxation of the original rules.

7. A Difficulty

There is one possible difficulty with the type of scheme outlined above which should not be overlooked. The comma-free conditions largely prevents a tRNA going on in the wrong phase; that is, displaced by 1, 2, 4, 5, ... bases, but a tRNA can quite happily bind with 5 base-pairs displaced by 3 bases from the proper position. If it persisted there indefinitely, and if the nascent polypeptide chains could not be transferred to the amino acid of this tRNA then further synthesis would be blocked. This difficulty is not so great if there is a weak nonspecific affinity, as we have assumed, between two adjacent tRNAs, but not between two tRNAs spaced one or more bases apart on the mRNA. Indeed it would be better if a single tRNA in the hf configuration did not bind too strongly so that it could float away from the mRNA after a moderately short time. If this were so polypeptide synthesis would only be delayed rather than stopped completely should it have gone on in the wrong place. The additional binding of the entering tRNA, with its amino acid, when in the *correct* position next to the previous tRNA (having the nascent chain attached) would help stabilise this important complex.

In the latter stages of the evolution of the code a primitive ribosome might make it unnecessary for a tRNA to interact with more than three base pairs and all comma-free constraints would then be removed. At the same time modification of the anticodon loop might remove unwanted pairing outside the anticodon triplet itself, as is found in many tRNAs today. Once the comma-free restraints were removed

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Darwin contrasted artificial selection with natural selection in his "Origin of Species." He states:

> Man can act only on external and visible characteristics; nature if I may be allowed to personify the natural preservation or survival of the fittest cares nothing for appearances, except insofar as they are useful to any being.

This history of science shows that Darwin did not know nor understand the genetic constraint placed on the degree of inherited variability. Gregor Mendell's work on the independent assortment of genes passed through Darwin's hands unread.

Therefore, Darwin's theory is the simplest construct that explains the observed similarity between species and the variation within species. The explanation he offers rests on the belief that the observed characteristics are inheritable and the number of progeny an organism leaves behind reflects its ability to survive as well as to mate in a particular natural environment.

Though Darwin clearly states in the quote given above that nature cares nothing for appearances, in actuality the competition he describes is phenotypic. The phenotype is that part of the organism that can be acted upon by the environment. In most cases it is the whole organism. The definition of phenotype as an expression of genotype was developed by the neo-Darwinians. The discovery of mutation and its later localization in DNA allowed an explanation of inheritable variation.

It is at this point we can ask ourselves the question, "What are the phenotypic characteristic of nucleotide sequences or what are the phenotypic characteristics of the genotype?"

The neo-Darwinian concept of evolution is as follows: a random mutation occurs in DNA. It is transcribed into mRNA, it is then translated into a variant protein. This protein affects metabolic or structural components in such a way as to create some change in the whole organism.

Whether that variant organism's genes are passed on depends on its competitive advantage to the other organisms in leaving progency.

The environmental conditions in which the competitive or mating takes place determine whether that variant organism's genetic contribution survives. If one samples that progeny population and finds that the variant organism's traits have become a significant proportion of the new population, then a neo-Darwinian would insist that the variant characteristic has conferred a selective adaptive advantage—even if he doesn't know what that advantage is.

Non-Darwinians have challenged the neo-Darwinian interpretation by saying that the fixation of a gene in a population is a consequence of small population size and drift. That is if an individual is a variant in a population of 100 individuals then the frequency of the gene he carries is 1 percent of the population. If he and two other individuals move to another island then the frequency of that gene is now 1 out of 3 or 30 percent.

No selection has occurred to increase the gene frequency simply by reduction of the effective breeding population size. These mutations that are not selected, or neutral mutations, according to Kimura, are those which have either synonymous codon assignments and/or are similar amino acid replacements in proteins.

This non-Darwinian theory quantitatively explains the constancy of mutation rate and the high degree of protein polymorphism.

a previously selected sequence also imposes a historical constraint on progeny sequences.

Genotypic selection is to artificial DNA sequence selection, or recombinant DNA work, as natural selection is to artificial breeding. Therefore a DNA sequence which has survived in a milieu of let us say mammalian DNA polymerases, mammalian RNA polymerases, mammalian tRNA, et cetera, will have a hard time adapting to an *E. coli* environment, with *E. coli* polymerase I, II, III. *E. Coli* RNA polymerase, *E. coli* tRNA, and so forth. The machinery of expression imposes constraints on that which is to be expressed.

For example, if a Congressman wishes to introduce a bill which is of great benefit to the public at large he must first demonstrate to each committee, Congressman, and aides how that bill is of direct benefit to them individually or their constituents before that bill has a chance to become law.

So, too, with DNA sequences. DNA sequences must first have all the proper structural and syntactical characteristics for replication, transcription, and translation before the protein products are made. DNA polymerases will replicate certain sequences better than others; only those sequences have a chance of being transcribed. RNA polymerase will recognize certain sequences more efficiently than others, only those will be expressed; and, ribosomes will bind certain sequences and not others, only those that are bound have a chance to be translated. Transfer RNA will interact with codons in their context, et cetera.

My perspective of the chance of an extreme taxonomic cross of DNA expressing its information, is the equivalent of a bill passed in the Korean Congress becoming U.S. law. It would require careful planning and extreme manipulation and if passed, irrelevant.

Mr. THORNTON. I think your example is a good one.

Dr. PIECZENIK. It is a double-edge example.

Therefore, given the perspective of genotypic selection the hazards, as well as the benefits, seem less dramatic. However, there is the observation that DNA is a historical molecule and may contain vestigial information that goes back 4 billion years. It is the expression of vestigal sequences that may now become a reality.

The consequences of vestigial or even random expression of small polypeptides is unknown and yet highly likely at the present stage of technological competence.

At present, I do not see the clear and present hazard or benefit from artificial DNA selection. DNA recombinant work will be a small part of significant nucleic acid research. Most of the significant work will revolve around studying naturally occurring nucleotide sequences.

I believe the only contribution that this round of experiments will demonstrate is that messenger RNA and tRNA coevolved.

At present I would prefer to see a clean hands policy in regard to the regulation of recombinant DNA work. That is:

One: Those involved in regulating, as well as advising which experiments are to be sanctioned should not be scientists with a financial, whether direct or indirect, interest in the area.

Two: That the regulating board consist of informed lay public, journalists, political representatives, union representatives, and scientists not involved in nucleic acid work, genetics, or molecular biology.

Why does DNA consist of four nucleotides? The reason we can ask "why" questions is we live and analyze these molecules as if they belong to the construct developed by Darwin.

Mr. THORNTON. Do we ask why they are polypeptides?

Dr. PIECZENIK. Yes. That is a reasonable question. We can ask that. Yet basically we are talking about chemicals. That we can ask that why question implies that we are asking it within a construct and that construct is the dogma of evolution.

Scientists that don't work within this construct don't ask those questions.

Mr. THORNTON. Well, I think perhaps you are using the word "dogma" in somewhat a different——

Dr. PIECZENIK. It is not a political dogma.

Mr. THORNTON. I suppose, like Lewis Caroll, we will have to arrive at some definition of what the word means, rather than to assume just what either of us intends it to mean.

Dr. PIECZENIK. There is a concept of evolution called the Red Queen model that comes from "Alice in Wonderland" and it says that in order for some person to gain, someone else has to lose. Much like in the Red Queen land, you have to run twice as fast to stay where you are.

Mr. THORNTON. There are methods which have been suggested which have later been discredited. I believe Lysenko's theories, which set back Russian biological research by many years suggested that acquired characteristics could be inherited. I wondered if a bacteria, *E. coli*, which acquires a characteristic by genetic manipulation or insertion of genetic information into its structure, can pass on that trait.

And if so, is Lysenko right but on a different level? Is that an acquired or added trait?

Dr. PIECZENIK. Lysenko did not believe that DNA was the genetic material. The acquired characteristics were crossed phenotypic characteristics which he felt then would be genotypically inheritable.

When do you insert DNA and it becomes adaptive within the bacteria and it survives in the bacteria——

Mr. THORNTON. Is that an acquired characteristic for that particular bacteria?

Dr. PIECZENIK. It is acquired by the bacteria or given to it.

Mr. THORNTON. It is inheritable?

Dr. PIECZENIK. Yes.

Mr. THORNTON. In the resarch which you have done and the testimony which you have brought to our attention, are you operating upon a theory that perhaps the same rules of inheritability, adaptability, survival which apply in gross to organized species also may apply at the molecular level?

Dr. PIECZENIK. That is the idea I have introduced.

That is the idea that I believe is correct and should be tested.

Mr. THORNTON. I think it is an interesting concept and I am looking forward to further discussion with the other panelists. Mr. Hollenbeck?

Mr. HOLLENBECK. Thank you, Mr. Chairman. Doctor, I would like to expand more upon your answer to the chairman's last question. I would like you to address yourself to the statement you made at the beginning of page 4 that at present you do not see the clear and present hazard or benefit from artificial DNA selection.

Extramural activities—(memberships, honors etc.):
American Association for Advancement of Sc.
Endocrine Society and International Endo Soc.
Society for Exp Biology and Medicine.
Central Society for Clinical Research.
Sigma XI.
Society Clinical Invest.
Society for Study of Reproduction.
American Society Biological Chemists, member.
Lecturer, Laurentian Hormone Conference, 1969–
National Pituitary Agency, Conadotropin Subcommittee, 1970–
American College of Physicians, Research Fellow, 1957–58.
Journal of Endocrinology and Metabolism, editorial board, 1968–73.
NIH, Reproduction Biology Study Section, Chairman 1972, 1970–73.
National Pituitory Agency, medical advisory board, 1970–73.
The Endocrine Society, council, 1974–
Procedural Society Experimental Biology and Medicine, editorial board, 1973–
NICHD, population centers committee, 1974–
Ford Foundation, advisory review committee, 1975–
Research Interests:
Humau Genadotrophic Hormones.
Hormone Receptors.

STATEMENT OF DR. ROBERT J. RYAN, DEPARTMENT OF MOLECULAR MEDICINE, MAYO MEDICAL SCHOOL

Dr. RYAN. I do not regard myself as having expertise in the area of recombinant DNA. I am an endocrinologist with a particular interest in reproduction. My interest in recombinant DNA arose from a serendipitous event as described in my written statement. In summary, the written statement makes the following points:

One. The bacterium, *pseudomonas maltophilia*, specifically binds the hormone human chorionic gonadotropin—hCG—with properties similar to the hormone receptor site found in mammalian ovarian tissue.

Two. This binding phenomenon has been found with *pseudomonas maltophilia* obtained from two sources and with *brucellus suis*, but not with a variety of other bacteria.

Three. The culture media from *pseudomonas maltophilia* gave evidence for bacterial production of an hCG-like material in several assay systems—radioimmunoassay, radioreceptor assay, stimulation of rat ovarian adenylyl cyclase enzyme activity and progesterone production.

Four. Other investigators had reported production of an hCB-like molecule by bacteria.

Five. Efforts to purify the hCG like activity from the pseudomonas culture media lead to the discovery of a protease enzyme.

Six. The bacterial protease, as well as other serine proteases, was able to mimic the effects of hCG in the assay systems previously mentioned.

Seven. Because of the protease activity, as well as change and size differences between this molecule and hCG and the two submit nature of hCG, we doubt that this phenomenon represents an example of a recombinant DNA.

Eight. Because of the importance of the problem and because all available data cannot be proven to be due to protease activity, we are exploring the possibilities of a plasmid and the presence of mammalian DNA within the bacterial DNA.

[The full text of Dr. Ryan's statement follows:]

cells from a variety of species. Moreover, this phenomenon was restricted to a few strains of bacteria. Binding was found with Pseudomonas maltophilia (either our isolate from the follicular fluid or the strain obtained from the American Type Culture Collection which was originally isolated from a patient with cancer) but not other Pseudomonas, E. coli, etc. We have recently, however, found an hCG binding site on Brucella suis, an organism responsible for infectious abortion in swine.

These observations provoked us to ask why these bacteria have a binding site for a mammalian protein hormone? One interesting possibility was that the bacteria produce an hCG-like molecule which might serve as a mechanism for intercellular communication. This possibility seemed somewhat feasible since there were two reports in the literature concerning hCG production by bacteria.

Dr. Virginia Livingston reported in the Annals of the New York Academy of Science (Vol. 36, p. 569, 1974) the isolation of a microorganism from many patients with cancer that produced an hCG-like material. The Livingston organism had variable characteristics with respect to its staining properties and she named it Progenitor cryptocoides. Doctors Cohen and Strampp reported in The Proceedings of the Society of Experimental Biology and Medicine (Vol. 152, p. 408, 1976) the isolation of an organism from the urine of a patient with cancer that produced a material that had the following characteristics of hCG:

1) Cross reaction in a radioimmunoassay for hCG,
2) Competition in a receptor assay for hCG,
3) In vitro stimulation of testosterone secretion by rat testicular cells, and
4) The presence of carbohydrate.

was great variability from one batch of media to another. Second, the various activities described above were associated with molecules of differing sizes, none of which were the same size as hCG. These inconsistencies appear to be due to the presence of a proteolytic enzyme in the culture media. Furthermore, the proteolytic enzyme in the media, as well as other serine proteases from both bacterial and mammalian sources mimic hCG in several of the assays mentioned above. Specifically, they:

1) Decrease binding of ^{125}I-hCG to antibodies to hCG and to rat ovarian receptors for hCG unless a protease inhibitor is present, and
2) They activate the adenylate cyclase enzyme in the rat ovary as described above and again this action is blocked by protease inhibitors.

These observations have made us somewhat skeptical about the bacterial production of hCG. This skepticism is enhanced by several additional considerations:

1) As pointed out above, the activities found in the culture media do not correspond in size (or charge) to the properties of hCG.
2) The hCG molecule is composed of two subunits and both are required to be associated to form the active hormone. Available data suggest that these subunits are synthesized as a consequence of two separate genes. If this proves to be true, then it may require that a strain of bacteria acquire two genes rather than one.

The above narrative illustrates a well-known fact of scientific life that is often overlooked in preparing budgets to support research. You cannot predict where new observations will arise nor can you accurately foretell the consequences and relevance of new observations until they have been examined in some detail. Unfortunately, the earmarking of Federal research funds in the biomedical area to specific diseases and practical missions has limited the funding to areas of basic research where these new observations and insights are perhaps most apt to arise. One example of this is the decrease in funds available for support of research in Endocrinology from the NIAMDD. This whole Institute, as well as the Institutes of General Medical Sciences and Allergy and Infectious Disease, are suffering financial restrictions.

Robert J. Ryan, M.D.
Chairman
Department of Molecular Medicine
Mayo Medical School

gesting there is a possibility that the bacteria can use this hormone or benefit from it?

Dr. RYAN. Well, what we are suggesting here—this is purely speculative and it is out of my area of competence—but how does a bacterial culture know when to grow and when to shut off growth? Maybe there is a need for some kind of a signal between bacteria to say let's all divide or let's die. It may be some other subtler kind of communication. What we are suggesting is that the presence of a binding site and a hormone, if you will, might be a means for executing this communication function.

Mr. THORNTON. I doubt that the self-destruct syndrome would be inheritable. [Laughter.]

Dr. RYAN. That I could not answer.

Mr. THORNTON. Our next witness is Dr. Patricia Charache. We are pleased to have you with us. Dr. Charache is at Johns Hopkins Hospital.

We would like to have your initial presentation at this time.

STATEMENT OF DR. PATRICIA CHARACHE, JOHNS HOPKINS HOSPITAL

Dr. CHARACHE. I was asked to comment on several aspects of infectious diseases, and infection control that impact upon recombinant research.

I am associate professor of medicine and laboratory medicine and the medical director in charge of microbiology laboratories at Johns Hopkins Hospital. I am a member of the Biohazards Safety Committee of Johns Hopkins University, which is under the direction of Roger M. Perriot and responsible for safety of DNA research at Johns Hopkins. Because of the range of topics that can be considered in infection control relevant to DNA research, I am going to comment very briefly on a range of subtopics which could be explored in further detail as desired.

I have also suggested to Dr. McCullough several other people with extensive experience in epidemiology and infection control who perhaps could contribute a great deal to such hearings.

In consideration of the risk of infection, given an accidental spill of bacteria, I think it is critical to appreciate that bacteria are not all alike and that they differ very widely in risk of colonization or infection, just as other species vary in the degree of hazards which they present.

As an example, tigers are more hazardous than guinea pigs, and the same is true relatively in terms of bacteria. The reasons for the differences in biohazard between microbes are well understood in some instances but very poorly understood in others.

Bacteria can induce infection through disparate organisms. A noninvasive organism can produce disease through toxin production as in the case of botulism. DNA research involving such organisms has been proscribed under the NIH guidelines so that *E. coli* cannot be used to produce a lethal toxin.

There are toxin-producing strains of *E. coli* that appear in nature, that appear to be plasmid associated, and that can cause a cholera-

Bacteria carry the plasmids that contain the ability to transfer antibiotic resistance. Over 20 percent of those acquired infections in some hospitals are now acquired by such genetically altered strains. The plasmids convey genetic information that leads to resistance to multiple antibiotics. We have had patients that are resistant to all currently available effective antibiotics, returning us to pre-1930's level of available care. The prevalence of plasmids that convey multiple drug resistance is influenced by antibiotic usage; the more antibiotics are used, the more likely this reaction is of occurring. Such plasmids, however, have been found in nature in bacteria that were isolated before antibiotics had ever been discovered by man.

It has become very clear that due to spontaneously occurring plasmid-associated resistant strains, old infectious disease control systems must be modified because these measures were primarily designed to permit control of individual strains of bateria rather than plasmids which are a relatively newly recognized problem in infectious disease control. This required attention goes beyond that of DNA recombinant research problems, and involves agriculture and commerce as well as research.

Control of possible DNA recombinant infectious problems is being approached through implementation of the NIH guidelines. Application of these guidelines in the university setting can be made precise and effective. In our institution, about 20 projects have been reviewed. About half of these have been approved as submitted. Most of the remainder have been approved after correspondence, although some required a change in protocol to different microbial plasma combinations, and others were postponed pending availability of improved laboratory facilities.

We review all proposals annually, more frequently if changes are proposed. The biohazards surveillance officer certifies the facility and personnel as appropriate for the work proposed, reviewed on an annual basis according to written current guidelines.

As written by the NIH committee these have been found to be implementable. I do not wish to imply by this that I don't feel that they should never be modified and extended. But they have been practical as designed by the microbiologists and other scientists who are employing these techniques.

In summary, *E. coli* is a relative nonhazardous organism. Strains designed for improved recombinant research are even safer than the wild-type strains. Genetic transference is important in the uncontrolled state as well as the laboratory setting. DNA recombinant control in their current NIH-recommended form appear to be practical and enforceable.

Thank you.

Mr. THORNTON. Thank you very much. What capacity for research do you have at Johns Hopkins? Do you go to P3 or P4 levels of containment?

Dr. CHARACHE. We go to P3 but not to P4. The P4 facilities are to be limited in the number of institutions that will be using them. We have six laboratories working in DNA recombinant research.

Mr. THORNTON. Thank you very much for your excellent testimony. I am looking forward to further questions and exchanging views after

that three or four distinct strains of *E. coli* reside together in the bowel; they remain and multiply for periods of 2 to 4 months being replaced from time to time by other *E. coli* strains.

The factors which are responsible for this colonization are not fully understood. In addition to the resident *E. coli* flora, transient strains from our food and water appear, but these do not persist and are isolated from the stool for only short periods of time.

It is difficult to predict how a particular *E. coli* with normal cell wall components will behave when introduced into the gastrointestinal track of a given individual. Such an organism may not be isolated from the stool or it could become a resident strain.

As an example, table 1 gives the results of an experiment done in collaboration with Dr. R. B. Hornick's group at the University of Maryland School of Medicine in which an *E. coli* strain originally isolated from a healthy laboratory worker was fed at two dose levels to healthy volunteers.

It is evident that multiplication occurred and in some individuals the organism was excreted for a long period of time. In contrast, Dr. E. S. Anderson obtained different results when he fed comparable doses of the common laboratory strain *E. coli* K–12 to volunteers in England. None of the individuals shed this particular strain for more than 7 days.

Strain K–12 is deficient in cell wall components and is the parent *E. coli* from which Dr. Curtis prepared strain 1776, the strain to be used as a host for recombinant DNA experiments.

While most strains of *E. coli* are considered to be nonpathogenic, certain strains may be isolated from the bloodstream of patients with underlying illnesses, others are the most common cause of urinary tract infections and additional strains produce diarrheal disease. The special attributes which *E. coli* must possess to cause bacteremia or urinary tract infections are only now being studied. On the other hand, there is information available concerning the mechanisms involved in *E. coli* induced diarrheal disease.

The organism either must be able to multiply in the small intestine and elaborate an enterotoxin or must be able to penetrate the intestinal epithelium and multiply in the tissue.

When these diarrheal disease mechanisms were defined, attempts were made to confer pathogenicity on originally avirulent *E. coli* strains. Dr. H. Williams Smith in England transferred both the ability to elaborate K–88 antigen—required for the organism to reside in the small intestine of piglets—and the ability to elaborate enterotoxin to certain avirulent strains of *E. coli*.

He showed that these laboratory-constructed organisms caused diarrhea in piglets. However, when these same two virulence factors were incorporated into *E. coli* K–12, this strain failed to multiply and remained nonpathogenic.

Clearly, additional attributes are required to render *E. coli* K–12 pathogenic. Our group at Walter Reed has been attempting to prepare safe oral vaccines against bacillary dysentery. We have transferred the ability to synthesize cell wall components of virulent *Shigella flexneri* 2a to *E. coli* K–12. Not only did this hybrid strain fail to cause disease, but when fed to volunteers—again in collaboration with Dr. Hornick—it was shed, table 2, in the stool to no greater extent

would have been identified and reported if they had been responsible for clinical disease in the surrounding population. It seems unlikely to me that the laboratory-altered weakened E coli K–12 strain will escape from a properly contained facility.

Mr. THORNTON. No pattern has been identified, however, which would lead you to that conclusion?

Dr. FORMAL. The only evidence we have is the negative data which I have just cited. The Fort Detrick laboratories have worked for a long time with agents causing such diseases as Rocky Mountain spotted fever, plague, tularemia, and anthrax. Fort Detrick scientists have had close liaison with the local hospital and the local health authorities in order to be made aware of any unusual disease in the community. Yet, not a single case of disease in the community. Yet, not a single case of disease traced to these laboratories has occurred in the town of Frederick, Md. Other laboratories work with additional highly lethal agents. Llassa fever is a good example. There is no evidence of escape or organisms from these laboratories.

Mr. THORNTON. Lassa fever has been studied only under the P–4 conditions, is that not correct?

Dr. FORMAL. I mentioned under proper containment facilities. Even there, Mr. Chairman, you work with dysentery bacilli at our laboratory at Walter Reed.

None of the family members of our laboratory workers have ever gotten bacillary dysentery. We have monitored the families very carefully over 20 years and we have not had a case. I think it is difficult to say that we will never have a case.

Mr. THORNTON. Is it your thinking that the reason for the failure of E coli K–12 which has had pathogenic characteristics added to it—maybe not in the sense we are talking about here, but in other biological senses—because of the failure of the organism itself to survive?

Dr. FORMAL. Our present evidence would indicate that, yes, sir.

Mr. THORNTON. Is there any reason for concern that some characteristics of the organism might be picked up by other E coli which do not have the K–12 weaknesses of the cell wall, thereby creating a survivable E coli?

Dr. FORMAL. Yes. I think that there is legitimate concern that this might occur. There is evidence that E coli K–12 carrying a transmissible plasmid will transfer this plasmid to other members of the intestinal flora of volunteers. On the other hand there has been no evidence that transfer has occurred with the same E coli K–12 strain which harbors a nontransmissible plasmid. More work is required before one can be assured that the latter will not take place.

Mr. THORNTON. I think that is a very important distinction for us to make, between the transmissible plasmids and the nontransmissible ones which do occur. Do you have any further comment with regard to this distinction?

Dr. CHARACHE. Just to emphasize that point, in determining degrees of containment and degrees of risk, the question of which transmissible agent is employed is as critical as which recipient is used. These are being selected as being unlikely to cause propagation of an undesirable trait.

Mr. THORNTON. I think one thing that concerns many people who read the literature which is publicly available on this issue is the

I think that is a kind of genetic engineering which was not intended at all, but which nonetheless did occur.

Dr. CHARACHE. Perhaps I could also comment that the NIH guidelines have taken into account both points just raised, the question of the investigator taking antibiotics and the question of the use of antibiotic resistance as a marker.

The NIH guidelines proscribe an investigator performing DNA recombinant research personally during the time he is on antibiotics and for a period of time after he is off antibiotics. Also, you cannot use antibiotic resistance markers that do not naturally occur, and that have a potential for usefulness in the management of infectious diseases.

Mr. THORNTON. You referred to the NIH guidelines. I would like to ask whether those guidelines are generally in accordance with your perceptions of what would be necessary in the control of disease, or whether your perceptions may have been changed by the guidelines.

What I am asking is, do you as a professional find that the guidelines are on track with your perceptions of risk?

Dr. CHARACHE. I would say yes. I think they are extremely thoughtful and they do answer the problems which are raised by this type of research. I think they have been very useful for the institution as guidelines for how we might improve construction and practice.

There are a couple of areas in which perhaps they could be clarified. For example, the guidelines that people working with DNA recombinant research shall have training in aseptic technique. It might be helpful to specify how extensive that training should be.

Perhaps there should be some suggestions as to what is meant by that.

There might be also some statement indications that the annual review of these laboratories shall include monitoring of equipment such as the biohazard safety hood centrifuges, and so on to be sure they are still functioning as they were when they were put in.

Mr. THORNTON. I would like to ask each of the other witnesses to comment with regard to that question. Dr. Formal, what is your evaluation?

Dr. FORMAL. I think they are very conservative.

Mr. THORNTON. When you use the word conservative, do you mean restrictive or safe?

Dr. FORMAL. I used conservative in the best sense of the word. The guidelines given us the necessary degree of safety.

Mr. THORNTON. Mr. Hollenbeck?

Mr. HOLLENBECK. Just maybe to make it a little more expeditious, I will add another question on the chairman's question. It is this: What is your opinion as to whether or not the NIH guidelines would be effective in curbing wild experimentation or terrorist use of DNA or just some accidental experimentation as has been alluded to today?

I would like you to address yourself to that subject as well.

Dr. FORMAL. I think that we can never be insured against the possibility that terrorists might use these techniques. In regard to the problem of "wild experimentation," I believe that we shall have to put the responsibility for monitoring this work on the universities and the laboratories themselves. This will be the most efficient way to administer the work.

to some of the proteins that coat the DNA. To what extent are genes regulated and to what extent do you think that a recombinant DNA would be regulated or unregulated?

Would the proteins that cover that recombinant DNA inhibit its expression?

Dr. PIECZENIK. The question of a gene at the mammalian level and its relationship to a single piece of DNA, a contiguous piece of expresed DNA is still not defined.

A gene may be sequences of DNA at various places. Therefore, the actual direct interaction of a particular peptide with DNA or with a particular subset sequence of DNA may not affect the total gene as we see its final product. It may affect part of its expression. I think you are directing yourself to an analogy where protein molecules actually repress or activate the expression of RNA. This is used as an analogy from the prokaryotic system to the eukaryotic system but there is no direct evidence for exactly what expression is at the eukaryotic system.

This is the hope of genetic engineers. But they won't be isolating a gene. They will be isolating a piece of DNA. The gene may be expressed over many chromosomes because the gene is the inherited characteristic that we can measure.

Gene is a concept that is a genetic measurement. DNA is a biochemical observation. We know that genes are made of DNA. But a particular gene may not be a contiguous set of DNA sequences. So even isolating a particular piece of sequence may not be isolating that gene.

Mr. THORNTON. You just opened a window for me. I appreciate that additional bit of information. You are saying that a gene may consist of genetic information in the form of combinations on the DNA molecule, part of which may exist at one end of the structure and part at the other. Some move in the middle and then over here on the side, correct?

Dr. PIECZENIK. Dr. Ryan's protein may have two genes coding for it. Most likely they are not contiguous. Therefore if you wanted to isolate the gene for that particular product, you would have to have two plasmines and hopefully you will get the combination. In that combination, it will be expressed. A gene is a genetic measure and has the characteristics that if you take progeny, that characteristic can be bred and its source independently.

It is a measure at the progeny level, and genetics as opposed to DNA work requires the viability of the organism. A phage geneticist counts bacteria phage and from that number of bacteria tries to deduce back to what is happening at the DNA level.

Here we are talking about DNA molecules.

Mr. THORNTON. I understand.

Dr. PIECZENIK. A gene is a concept of viable expression. A gene at the eukaryotic DNA level is still quite undefined.

Dr. RYAN. Suppose you took a piece of DNA and put it into another organism. One would presume in that organism it would be coated by histones and acidic proteins to a greater or lesser extent. Do recombinant DNA's become coated with acidic proteins?

Dr. PIECZENIK. The histones don't coat the DNA according to the Kornberg method. DNA actually winds around the histones and the histones form a core. Histones don't act as a regulatory protein but as a structural component. It constrains DNA to a very characteristic pat-

DNA work. You outlined four areas in some detail but rather quickly. I would like you to expand for us on your thinking or on your philosophy behind that.

If you will, we have had some testimony in prior hearings as to the international effect of our stopping DNA research and so on. I would like you to try to relate that with the experiences you have had alluding specifically to any relations or procedures which they have in England for this type of research.

Dr. PIECZENIK. First, the regulation in England has been—I will speak on the idea of Dr. Brenner mainly. The English in their fashion decided to call it a pause instead of a moratorium, and instead of setting a set of guidelines, a large compendium of regulations and rules, they decided to leave it undefined.

However, they set up an administrative structure which they call GMAC, which is genetic manipulation advisory committee, and this is composed of an informed lay public, editors of scientific journals, union representatives, scientists that are not involved in genetic recombination.

This body meets and discusses and has final ruling on experiments proposed by another body called GMUC, genetic manipulators users committee, which is a lobby for scientists that wish to do the experiments.

They present the experiment they want to do to GMAC, and GMAC decides whether it should be done or not and at what level of safety. They have also given themselves much more freedom on the choice of vector and have not thrown away attachment site as we have in substitution for antibiotic resistance.

They are designing basically vectors in which the vectors themselves recombine out the restriction fragments that are necessary and encapsulate them within the bacteriophage. That means there is another level of containment.

The bacteria hopefully will be adapted—adaptive both for its ability to not survive in the environment as well as to require a particular nutrient in order to survive. There is a double cross-check.

Containment will be done in small boxes. Dr. Brenner made the analogy if we want to work in the cold, we can go into a cold room. But if you look at supermarkets they don't put their food in a cold room. They actually have open-air freezers in which, this cold air is contained. This work can be contained in very simple boxes. We know then what the hazards are.

We know how to define them. These boxes can be engineered and designed almost for any level of containment such that you are never in direct contact with the material you are working with. The question of fractionation probably can be avoided by designing experiments cleverly. Basically the English believe, I think, not to set down their set of regulations but to work on precedent and experience and in an adversary relationship.

Mr. HOLLENBECK. Are you basing your suggestion today on the English experience?

Dr. PIECZENIK. Somewhat. My suggestions reflect more the moral policy set down recently in our Government. There is a legal question of clear-and-present hazard. I think that the regulations were evolved around that legal issue. There is also legal concept that is called

research money, may have a useful effect in urging additional caution?

Dr. CHARACHE. I think one of my concerns is how these guidelines will be applied industrially and by other groups that are not controlled by Government funding. I would guess that responsible institutions will respond the way the scientific community has that are being reimbursed by NIH.

The NIH guidelines called to people's attention conditions which were suboptimum in microbiology laboratories of many types.

Mr. THORNTON. There have been institutional changes which resulted from the operation of the guidelines?

Dr. CHARACHE. Yes. These extend beyond the DNA recombinant research area. By using the Center for Disease Control criteria for P1, P2, P3, and P4 infectious agents and having established these thoughtful and conservative guidelines in terms of what constitutes a proper containment for these agents, we find that a lot of laboratories who were working with agents which should have been controlled better than they were controlled, and this is a spinoff of this procedure.

Mr. THORNTON. Who set up the operating procedures for Johns Hopkins Biohazards Committee?

Dr. CHARACHE. There has been a biohazards safety committee for many years. I don't know how long. I have been on it for 8 or 9 years. This involves all divisions of the university and has been expanded for the DNA recombinant work to include undergraduate school as well as the school concerned with health sciences.

The guidelines and the application of the NIH guidelines have been under Dr. Roger Herriott's direction. The committee is a very broadly based one which includes scientists from the school of medicine, undergraduate school, and so on.

Mr. THORNTON. Thank you for yielding.

Mr. HOLLENBECK. Dr. Pieczenik?

Dr. PIECZENIK. The question was whether funding and research is adaptive. I am a little surprised that in P3 facilities, undergraduate students will be working.

Dr. CHARACHE. It is their professors who are working on it.

Dr. PIECZENIK. That is the point about the fourth issue, what I call the head of laboratory role. Let the person with the legal responsibility be the one that does the experiment. I forgot to mention, in England it is a criminal offense punishable by 2 years in prison and unlimited fine if you violate the guidelines of a letter set down by GMAC. That regulation is assignable to a subofficer. But then he has punitive powers. It seems peculiar that I, who believe there is no hazard, should argue for more careful or direct responsibility.

Mr. HOLLENBECK. You are talking more about the nature of the experimentation than you are about the safeguards, isn't that correct?

Dr. PIECZENIK. Both.

Mr. HOLLENBECK. Your guidelines seem to be directed, though, at an advisory board of noninvolved scientists and the lay public having, say, over the nature of the experiment and, to a certain extent, over the regulations. You are not quarreling with present safety setups and present methods, is that correct?

Dr. PIECZENIK. No; I don't feel the NIH guidelines reflect a sufficient spectrum of use. I think they reflect the spectrum of use by the persons that put the guidelines together.

Dr. PIECZENIK. No. He can then simply suggest the experiment he wishes to do to a head of a laboratory in which he has confidence.

Mr. THORNTON. Beethoven was able to write music although he could not hear it, isn't that correct? He should not be able to if he cannot hear it, for your theory to be accepted.

Dr. PIECZENIK. He could write music and he could internally hear it.

Mr. THORNTON. But he could not physically hear it.

Dr. PIECZENIK. Actually he could hear it because he has induction from the piano to the bone structure. [Laughter.]

Mr. THORNTON. I am not sure that anyone here can now testify as to whether Beethoven heard his own music internally or not, but according to reports he did not hear it physically. At least that is the historical version.

Dr. RYAN. I am sympathetic to your point of view, but I think what you can require is that the Senior Scientist at least be present at the experiment.

Mr. THORTON. Oh, yes; and completely accountable for the work. I don't think that I would disagree at all as to the purpose which you are trying to express, that is, to require strict scientific accountability for the work which is pursued. That does not necessarily mean that this scientist must physically go out to Pittsburgh or wherever it is done and blow the glass to make the test tube which he uses for part of the experiment.

Dr. PIECZENIK. The recombinant work is trivial technology. The tricky part is analyzing the product you have made. Actually restricting the fragments can be done by an undergraduate. It does not require great competence. The point is that perhaps this would force heads of laboratories to decide very carefully whether they want to gear up their laboratories to do this work.

If you are going to offer a scientist a $10 million laboratory to do recombinant work or $15,000 to analyze nucleotides, he will say, I will do the recombinant work.

I don't think the scientific validity has been demonstrated for the work. I have not seen an experiment that has been proposed using this technology——

Mr. THORNTON. Are you saying that a reverse Gresham's law applies, that heavily funded research drives out other types of research?

Dr. PIECZENIK. Yes. Crick's grandfather published a manuscript with Soddy saying that overfinancing in science has a tendency to kill it.

Mr. THORNTON. One other expression of my concern is that you would eliminate scientists from the panel which you suggest. You would not have those who were most informed about the field involved?

Dr. PIECZENIK. The question of most informed is a question of how much do we know about the area at this stage.

Mr. THORNTON. The regulating board you propose consists of informed lay public, journalists, union representatives, and scientists not involved in nucleic acid work, genetics, or biology.

Dr. PIECZENIK. That is people without an ax to grind.

Mr. THORNTON. Well, do you assume that anyone who has knowledge of this field necessarily adopts a philosophical or political viewpoint toward the research, as distinguished from pure scientific inquiry? Is that the reason?

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

THURSDAY, APRIL 28, 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 10:10 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.

Good morning. We are continuing today our hearings on the science policy implications of the DNA recombinant molecule research issue.

This is our fifth day of hearings in this series. We have touched upon today's topic in earlier hearings but we would like to provide a forum for a fuller decision.

Today, we are going to be discussing the many aspects of DNA recombinant molecule research which are of interest or concern to industry, the private sector.

I would now like to recognize the ranking minority member of our subcommittee, Mr. Hollenbeck, who will introduce our first witness this morning.

Mr. Hollenbeck.

Mr. HOLLENBECK. Thank you, Mr. Chairman.

We are fortunate to have with us today two gentlemen from the Pharmaceutical Manufacturers Association who have a background and knowledge in the field we are concerned with today.

They have prepared testimony which we have had the opportunity to see in advance, and I would like to introduce, first, Dr. John G. Adams, who is the vice president for scientific and professional relations, and Mr. Bruce J. Brennan, vice president and general counsel for the Pharmaceutical Manufacturers Association.

Welcome, gentlemen. I would like to join in welcoming you to the subcommittee and to express our appreciation for the prepared testimony which you have submitted.

Without objection that prepared testimony will be made a part of the record in its entirety, and I would like to ask you now to proceed to summarize and give us your views on this issue.

[Biographical sketches of Dr. Adams and Mr. Brennan follow:]

BRUCE J. BRENNAN

Born: November 24, 1930

Education: Holy Cross College, Georgetown University (A.B. 1953)

Legal Education: Georgetown University Law Center (LL.B. 1959)

Professional Background:

1960-1963	Trial Attorney in Office of General Counsel, Food and Drug Administration and Bureau of Deceptive Practices, Federal Trade Commission
1964-1969	Private practice in Washington, D. C., specializing in matters relating to the Federal control of foods, drugs, cosmetics and advertising
April 1969 to present	Vice President and General Counsel of the Pharmaceutical Manufacturers Association

Memberships:

American Bar Association, Chairman, Drug Law Committee, Section of Corporation Banking and Business Law, 1970-1972

Recent Activities and Publications:

Member of U. S. Delegation to United Nations Commission on Narcotic Drugs, January 1970, Geneva, Switzerland

Editorial Advisory Board, Food Drug Cosmetic Law Journal

The Right to Self-Medication -- A Continuing Conflict Between Congressional and Agency Policy, 23 Food Drug Cosmetic Law Journal 487 (October 1968)

Federal Regulation of the Drug Industry: Proceedings, Short Course on Drug Abuse, Southern Methodist University School of Law (April 1970)

The Need for Cooperation of Industry, Physicians and Government in Regulaton of Medical Devices, The Business Lawyer, Volume 26, Page 365 (November 1970)

Self-Evaluation -- Legal Aspects and Scope: Proceedings, Conference on Drug Efficacy Evaluation and Self-Evaluation by Pharmaceutical Industry, University of Wisconsin (October 1971)

STATEMENT OF DR. JOHN G. ADAMS, VICE PRESIDENT, SCIENTIFIC AND PROFESSIONAL RELATIONS, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, ACCOMPANIED BY BRUCE J. BRENNAN, VICE PRESIDENT AND GENERAL COUNSEL, LEGAL, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Dr. ADAMS. Thank you, Mr. Chairman and members of the committee.

This is a brief statement, Congressman Thornton, and if you have no objection, I will follow the text very closely.

Mr. THORNTON. Very good.

Dr. ADAMS. I am John G. Adams, vice president for scientific and professional relations of the Pharmaceutical Manufacturers Association, an organization of 129 firms that discover, develop, manufacture, and market most of the prescription drugs and a large percentage of the diagnostic reagents and medical devices available in the United States.

Accompanying me is Bruce J. Brennan, PMA vice president and general counsel. We appreciate the opportunity to appear before the subcommittee to offer our comments.

It is important, we believe, to place the involvement of the drug industry in recombinant DNA research in proper perspective in order to avoid any misinterpretation or misunderstanding of our position such as has been expressed in hearings before this subcommittee and in articles or statements which have appeared in the lay press and elsewhere.

At present three PMA member firms are directly engaged in such research, and three other member firms are supporting academic research. All of them are committed to voluntary compliance with the NIH guidelines.

The PMA became directly involved in discussions concerning recombinant DNA research on June 2, 1976, at a meeting convened by Dr. Frederickson of the National Institutes of Health. As a spokesman for the PMA at the June 2 NIH meeting, I indicated that copies of the NIH guidelines would be immediately referred to an expert committee of drug industry scientists for study and comment and that our comments would be reported to NIH promptly. I also indicated that a survey of PMA member firms would imemdiately be undertaken to determine the extent of their involvement in DNA research, either in their own facilities or through grant or contract support.

The results of these two activities were made public in hearings before the Health Subcommittee of the Senate Labor and Public Welfare Committee in September of 1976, and were provided concurrently to NIH officials. Formal comments on the guidelines were submitted to NIH in November in response to the Federal Register notice of July 7, 1976.

We also testified at hearings convened by the attorney general of the State of New York in October of 1976, and most recently in hearings convened by the Subcommittee on Health and Environment of the House Interstate and Foreign Commerce Committee, the Subcommittee on Health and Scientific Research of the Senate Com-

Statement on Recombinant DNA Research
on Behalf of the
Pharmaceutical Manufacturers Association
Before the
Science Advisory Board
Environmental Protection Agency
April 5, 1977

Mr. Chairman and Members of the Committee:

I am John G. Adams, Vice President for Scientific and Professional Relations of the PMA, an organization composed of 129 member firms that discover, develop, manufacture and market most of the prescription drugs, and a large percentage of the medical devices and diagnostic products available in the United States. I am pleased to appear before the Committee today and offer our comments on the areas of inquiry which were outlined in the Federal Register notice of March 16, 1977. My comments will be brief, but I hope responsive to your request.

Since the initial meeting of industry representatives with officials of the National Institutes of Health on June 2, 1976, we have carefully followed and closely cooperated with various federal government agencies, including the Departments of Health, Education, and Welfare and Commerce in their efforts to develop sound public policy on the subject of recombinant DNA research. We have also testified at hearings convened by the Subcommittee on Health of the Senate Labor and Public Welfare Committee and the Attorney General of the State of New York and, more recently, by the Chairman of the Subcommittee on Health and Environment of the House Committee on Interstate and Foreign Commerce. We shall again testify tomorrow before the Subcommittee on Health and Scientific Research of the Senate Committee on Human Resources, the new designation for the former Subcommittee on Health chaired by Senator Kennedy.

In the case of the drug industry, it is important for the Committee to bear in mind the vast experience we have accumulated in the handling of hazardous biological materials, such as are involved in the production of vaccines and other biological products. Our facilities and personnel are probably the most sophisticated in the entire scientific community in this type of research and production technology and the outstanding record of the industry in the handling of these materials offers testimony to that expertise and experience.

Our comments in response to the two specific areas of inquiry by the Committee will necessarily be brief.

It is our considered opinion that appropriate legislation and regulation will provide the immediate safeguards which are needed in this emerging field of research. We are satisfied that the necessary elements of such legislation have been incorporated into the Report of the Interagency Committee. We shall offer specific comments on the Administration Bill, S. 1217, introduced by Senator Kennedy on Friday in tomorrow's hearings, and I shall be pleased to make copies available to you. The Bill provides essential requirements for licensing of facilities, registration of projects, interim and final standards for physical and biological containment, inspections and reports. Responsibility for compliance and enforcement of the proposed legislation and regulations is vested in the Secretary of HEW. Further, there is a requirement in the Bill for consultation with a number of government departments and agencies, including the Environmental Protection Agency. Full compliance and enforcement of the physical and biological containment provisions of the existing NIH Guidelines, or as they may be modified in regulations promulgated following the

C. Joseph Stetler, President
Pharmaceutical Manufacturers Association

Before the

Subcommittee on Health and Scientific Research
Senate Committee on Human Resources

on

S. 621, S. 945 and S. 1217, 95th Congress

April 6, 1977

Mr. Chairman and Members of the Committee:

I am C. Joseph Stetler, President of the Pharmaceutical Manufacturers Association, an organization composed of 129 member firms that discover, develop, manufacture and market most of the prescription drugs and a large percentage of the medical devices and diagnostic products available in the United States. Accompanying me are Dr. John G. Adams, PMA Vice President, Scientific and Professional Relations and Bruce J. Brennan, PMA Vice President and General Counsel. We are pleased to accept the Subcommittee's invitation to present our views on S. 621, S. 945 and S. 1217, 95th Congress.

Recombinant DNA Research, the subject of all three bills, offers great promise in many fields, including the treatment and prevention of various diseases. For this reason we feel that any legislation adopted should encourage as well as regulate such research.

Last September, we testified before your Subcommittee on the involvement of PMA member firms in Recombinant DNA research. At that time, we commented on the NIH guidelines of July, 1976, pointing out that with some minor modifications, the pharmaceutical industry would voluntarily comply with them.

S. 1217, 95TH CONGRESS

THE LEGISLATIVE PROPOSAL TO WHICH WE WOULD LIKE TO DIRECT OUR PRINCIPAL ATTENTION IS S. 1217, THE "RECOMBINANT DNA REGULATION ACT". WE FEEL THAT THE BASIC REGULATORY FRAMEWORK SET FORTH IN THAT BILL IS SOUND AND WOULD PROVIDE EFFECTIVE CONTROLS WHILE NOT INTERFERING EXCESSIVELY WITH THE RESEARCH PROCESS. WE AGREE THAT THE SECRETARY OF HEW SHOULD PROMULGATE STANDARDS CONCERNING THE PRODUCTION AND POSSESSION OF RECOMBINANT DNA.

DESPITE THIS GENERAL SUPPORT, WE ARE TROUBLED BY CERTAIN OF THE SPECIFIC PROVISIONS OF THE BILL. THE INTERAGENCY REPORT, WHICH THE BILL PURPORTS TO IMPLEMENT, WOULD APPLY THE CONCEPT OF LICENSING BY THE FEDERAL GOVERNMENT TO FACILITIES WHICH PRODUCE OR POSSESS RECOMBINANT DNA AND SUBJECT THE ACTUAL RESEARCH PROJECTS ONLY TO A REGISTRATION OR NOTIFICATION REQUIREMENT. YET, THE ACTUAL PROVISIONS OF S. 1217 WOULD APPEAR TO CREATE A DIFFERENT SITUATION.

ONE OF THE NECESSARY PREREQUISITES FOR OBTAINING A LICENSE UNDER THE BILL IS AN AGREEMENT AND A DETERMINATION BY THE SECRETARY THAT PRODUCTION OR POSSESSION OF RECOMBINANT DNA WILL ONLY OCCUR AS A PART OF A REGISTERED PROJECT. UNDER THE TERMS OF SECTION 6 OF THE BILL, THE SECRETARY WOULD REGISTER THE PROJECT ONLY IF THE REGISTRATION REQUEST IS ACCOMPANIED BY INFORMATION ADEQUATELY DESCRIBING THE PROJECT. WHEN THESE TWO SECTIONS ARE READ TOGETHER, THEY SEEM TO REQUIRE NOT ONLY PRECLEARANCE, THAT IS LICENSURE OF THE FACILITY BUT ALSO OF THE RESEARCH PROJECT.

WE SUGGEST THAT THE LICENSING PROVISIONS OF THE BILL BE LIMITED TO THE LICENSING OF FACILITIES. IT IS APPROPRIATE FOR THE SECRETARY OF HEW TO BE ASSURED THAT A FACILITY USED FOR RECOMBINANT DNA RESEARCH

COULD PETITION FOR RELIEF TO THE SECRETARY OF LABOR. AFTER AN INVESTIGATION, THE SECRETARY OF LABOR COULD ISSUE AN ORDER TO REINSTATE THE EMPLOYEE, PAY COMPENSATION, INCLUDING BACK PAY, AND ASSESS COMPENSATORY AND EVEN EXEMPLARY DAMAGES AGAINST THE EMPLOYER. THIS PROPOSED SYSTEM FOR HANDLING EMPLOYEE/EMPLOYER DISCRIMINATION COMPLAINTS SEEMS TO BE UNNECESSARY. CURRENTLY, THERE IS A RELATED BUT LESS PUNITIVE PROCEDURE AVAILABLE UNDER SECTION 11(c) OF THE OCCUPATIONAL SAFETY AND HEALTH ACT OF 1970 (29 USC, SEC. 660(c)). WE RECOMMEND THAT ANY PROVISION IN RECOMBINANT DNA LEGISLATION INTENDED TO SAFEGUARD AGAINST REPRISAL BY EMPLOYERS BE CONSISTENT WITH THOSE PROVISIONS.

THE PROVISIONS OF THE BILL WITH RESPECT TO ENFORCEMENT WOULD AUTHORIZE THE SECRETARY OF HEW TO DIRECTLY ASSESS CIVIL PENALTIES FOR VIOLATIONS OF THE ACT OTHER THAN THOSE RELATING TO EMPLOYEE PROTECTION. WE DO NOT OPPOSE A SYSTEM OF CIVIL PENALTIES BEING ASSOCIATED WITH VIOLATIONS OF THE BILL. HOWEVER, WE RECOMMEND THAT AN ACTION FOR CIVIL PENALTIES BE INITIATED BY THE GOVERNMENT IN A FEDERAL COURT PROCEEDING RATHER THAN IN AN ADMINISTRATIVE PROCEEDING BEFORE THE SECRETARY.

WE NOTE THAT THERE IS A PROVISION FOR JUDICIAL REVIEW REGARDING THE PROMULGATION OF STANDARDS UNDER THE ACT. HOWEVER, THERE IS NO PROVISION FOR JUDICIAL REVIEW OF ACTIONS OF THE SECRETARY CONCERNING THE ISSUANCE OR REVOCATION OF A LICENSE. WE WOULD HOPE THAT THIS IS MERELY AN OVERSIGHT BY THE DRAFTERS OF THE PROPOSAL. JUDICIAL REVIEW OF LICENSING REQUIREMENTS IS A MATTER OF DUE PROCESS WHICH IS PROTECTED BY THE CONSTITUTION AND SHOULD BE INCLUDED IN THE BILL.

FINALLY, WE WOULD SUGGEST THAT THE PRE-EMPTION SECTION BE AMENDED TO PROVIDE THAT THE SECRETARY "MAY" RATHER THAN "SHALL" EXEMPT A STATE OR SUBDIVISION FROM THE PROVISION OF SECTION 10(A).

THERE IS ALREADY SUFFICIENT AUTHORITY IN THE LICENSING AND OTHER PROVISIONS TO PRECLUDE MISUSE BY PRIVATE PARTIES.

THE OTHER PATENT RESTRICTION RELATES TO COMPLETE DISCLOSURE OF PROCESSES AND ORGANISMS IN THE PATENT APPLICATION. WE ASSUME THAT THIS PROVISION SUGGESTS SUBSTANTIALLY GREATER DISCLOSURE OF INFORMATION THAN WOULD ALREADY BE REQUIRED IN THE NORMAL PATENT APPLICATION. WE FEEL THAT THE DEMAND FOR SUCH DISCLOSURES WOULD ACTUALLY FORCE PERSONS HOLDING INVENTIONS TO GUARD THE RESULTS OF THEIR RESEARCH BY AVOIDING THE PATENT SYSTEM AND RELYING ON THEIR COMMON LAW TRADE SECRET PROTECTIONS. INSTEAD OF MAKING THEIR INVENTION KNOWN TO THE EXTENT THAT THE PATENT LAWS REQUIRE, AND, THEREBY AIDING OTHER INVESTIGATORS OR INVENTORS IN THE PROCESS, RESEARCHERS OR INDUSTRIAL FIRMS HAVING SUCH KNOWLEDGE WOULD CIRCUMVENT THE PATENT SYSTEM.

AS TO DISCLOSURE OF INFORMATION DEVELOPED IN THE RESEARCH PROCESS, WE OUTLINED OUR RESERVATIONS WITH THE DEPARTMENT OF HEW WITH RESPECT TO THE GUIDELINES ON RECOMBINANT DNA RESEARCH WHICH WERE PUBLISHED LAST SUMMER. WE ACCEPT AND SUPPORT THE CONCEPT OF INFORMING THE SECRETARY OF HEW THAT A FIRM OR INDIVIDUAL IS ENGAGING IN RECOMBINANT DNA RESEARCH AND OF PROVIDING INFORMATION AS TO THE TYPE OF PROJECT THAT IS BEING UNDERTAKEN AS WELL AS ITS GENERAL NATURE. IT IS IMPORTANT, AT THE SAME TIME, TO MAINTAIN THE CONFIDENTIAL AND TRADE SECRET STATUS OF PROJECTS OR DATA WHICH DESERVE THAT STATUS. WITHOUT THAT FORM OF PROTECTION, IT WOULD BE DIFFICULT FOR PRIVATE FIRMS TO JUSTIFY THE KINDS OF INVESTMENTS NECESSARY TO FINANCE THIS KIND OF RESEARCH.

THE NO-FAULT, STRICT LIABILITY PROVISIONS COULD VERY WELL CAUSE THE INSURANCE INDUSTRY TO REASSESS ITS ENTIRE COVERAGE FOR PHARMACEUTICAL COMPANIES OR OTHER FIRMS. IN LIGHT OF THE EXPERIENCE

BOTH S. 621 AND S. 945 TREAT VIOLATIONS OF THE ACT AS CRIMINAL OFFENSES. IN ADDITION, BOTH BILLS WOULD IMPOSE CRIMINAL PENALTIES AGAINST EMPLOYERS WHO DISCHARGE OR DISCRIMINATE AGAINST EMPLOYEES BECAUSE OF THE EMPLOYEE'S INVOLVEMENT IN PROCEEDINGS AGAINST THE EMPLOYER. WE FEEL THESE PENALTY PROVISIONS ARE TOO SEVERE FOR THE MANY TYPES OF ACTIVITIES WHICH THEY WOULD EMBRACE. WE SUGGEST A MORE DEFINITIVE SET OF PENALTIES THAT WOULD PERMIT INJUNCTION OR PERHAPS CIVIL FINES FOR MINOR OFFENSES AND RESERVE CRIMINAL PENALTIES FOR MORE SERIOUS OFFENSES OR IN THE CASE OF WILLFUL VIOLATIONS OF LICENSING OR STANDARDS PROVISIONS. CRIMINAL PENALTIES SHOULD NOT BE IMPOSED UPON EMPLOYERS SIMPLY BECAUSE OF EMPLOYMENT DECISIONS, EVEN WHERE SUCH DECISIONS ARE DETERMINED TO BE DISCRIMINATORY. THERE ARE ALREADY SUFFICIENT ENFORCEMENT PROCEDURES UNDER THE OCCUPATIONAL SAFETY AND HEALTH ACT OF 1970.

TITLE II OF S. 945, WOULD ESTABLISH A NATIONAL COMMISSION FOR THE STUDY OF RECOMBINANT DNA RESEARCH AND TECHNOLOGY, WITH MEMBERS TO BE APPOINTED BY THE SECRETARY OF HEW. THE COMMISSION WOULD STUDY THE APPROPRIATENESS OF CONTINUING RECOMBINANT DNA RESEARCH; DEVELOP GUIDELINES FOR ITS CONDUCT AND ADVISE THE SECRETARY CONCERNING ADMINISTRATIVE ACTION TO PUT SUCH GUIDELINES INTO EFFECT. IN VIEW OF THE WORK ALREADY COMPLETED BY THE NATIONAL INSTITUTES OF HEALTH AND THE INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH, WE QUESTION THE PRACTICALITY OF ANOTHER STUDY COMMISSION. FROM OUR READING OF THE MARCH 15 INTERIM REPORT OF THE INTERAGENCY COMMITTEE, IT WOULD SEEM THAT THE SECRETARY ALREADY HAS A WELL QUALIFIED ADVISORY BODY. THIS GROUP HAS SOUGHT THE COUNSEL OF EXPERIENCED EXPERTS FROM ACADEMIA AND FROM INDUSTRIAL CONCERNS. WE WOULD HOPE THAT IT WOULD CONTINUE TO DO SO AND WOULD THEREBY SATISFY THE OBJECTIVDS OF TITLE II OF S. 945.

Responses to Propositions and Questions In Preamble to S. 1217

1. Definition of Recombinant DNA Research

We have discussed the proposed new definition of recombinant DNA research with industry experts and have been informed that it is acceptable. The new definition differs technically in the introduction of the term "molecule" in addition to the term "segments of molecules". The new definition also includes research as distinguished from the more limited definition of the recombinant DNA molecule. It appears to refer to that research which involves the synthetic or unnatural recombination of DNA segments or DNA molecules. We have no objection to this redefinition but suggest that it could be stated somewhat differently for purposes of clarity.

2. Commission to Participate in DNA Research Decisions

We would advocate the creation of an "Advisory Council" composed of experts in the field of recombinant DNA research and bioethics, law and other nonscientific disciplines. DNA expertise should cover biomedical, agricultural and other scientific disciplines.

3. Scope and Nature of Statutory Standards

It was our belief that the use of the term "production or possession" was intended to regulate all activities involving recombinant DNA, including research and commercial development. We would, therefore, have no objection to including the term "research". Accordingly, the scope should include research, production and possession.

With respect to standards dealing with the qualification of the individuals conducting the research, we have reservations. It could result in governmental control of scientific qualifications and the

11. Information to be Submitted to Government and Disclosed to Public

We believe the name and address of the facility, the names of the research personnel involved, and an outline of the research project should be submitted to the government and, if deemed desirable, be made available to the public. We also believe that facilities should be subject to government inspection and reporting requirements. In any case, confidential proprietary information submitted should be given protection under specific provisions of the implementing legislation.

LICENSING OF FACILITIES

1. Delete Section 5 (a) (3)

2. Amend Section 5 (e) (5) as follows:

(5) has failed to comply with a request of the Secretary to inspect any portion of the facility, its operations, or its records, which are ~~related~~ designated in section 7, ~~to activities involving recombinant~~ DNA, or

3. Add new Section 5(f):

"Any person adversely affected by an action of the Secretary under this section may obtain review of the action in the United States Court of Appeals for the District of Columbia. The petition for review must be filed within sixty days of the action. Review shall conform to chapter 7 of title 5 of the United States Code."

INSPECTIONS

Delete Section 7 and replace with the following:

Sec. 7 (a) For the purposes of enforcement of the licensing requirements of this part, officers, employees, or agents designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator or agent in charge, are authorized to enter and inspect at reasonable times, in a reasonable manner and within reasonable limits any establishment licensed under section 5 or in which recombinant DNA is present or is being produced. Such an inspection may extend only to pertinent records, files, papers, facilities, equipment and other items in the establishment that are directly related to such license, possession or production to determine:

(1) whether the establishment conforms to the requirements for obtaining or holding a license under section 5; and

(2) whether the establishment conforms to any applicable standards established pursuant section 4.

(b) Upon completion of any such inspection and prior to leaving the premises, the officer, employee, or agent making the inspection shall give to the owner, operator, or agent in charge a preliminary report which summarizes any conditions or practices observed by him which, in his judgment, indicate a violation of the licensing requirements of this part. He shall also prepare a written final report of

EFFECT ON STATE AND LOCAL REQUIREMENTS

Amend Section 10 (b) as follows:

Upon application of a State or political subdivision of a State, the Secretary ~~shall~~ may exempt from subsection (a) a requirement of that State or political subdivision applicable to recombinant DNA activities if he determines that the requirement is, and will be administered so as to be, as stringent as, or more stringent than, a requirement under this Act. The Secretary may not withdraw any such exemption for so long as he finds that such requirement remains unchanged and continues to be so administered.

ENFORCEMENT

1. Amend Section 13 (b) (1) as follows:

(b) (1) Any person who violates a provision of this Act (other than in section 11) shall be liable to the United States for a civil penalty in an amount not to exceed ~~may be assessed a civil penalty by the Secretary of not more than~~ $5,000 for each violation.

2. Delete Sections 13(b) (2) and (3).

File - FA
DNA

April 4, 1977

The Honorable Paul G. Rogers
Chairman, Subcommittee on Health and Environment
House Committee on Interstate & Foreign Commerce
2407 Rayburn House Office Building
Washington, D.C. 20515

Dear Congressman Rogers:

During the course of our testimony on March 17, concerning H.R. 4759, 95th Congress, we suggested a number of amendments. In response to your request for a more definitive expression of our recommendations, we are enclosing specific suggested amendatory language. Some of these proposals are sufficiently different from provisions in the bill to require their being set forth in their own style. Others relate more directly to the provisions of the bill and are framed in the style of the various sections of the bill to which they relate.

We noted in our testimony the belief that effective controls on Recombinant DNA research can be instituted through registration and notification without the need for Federal Project Licensure. While we still feel that that is the preferable approach we have attempted to draft licensure provisions which would apply to establishments at which Recombinant DNA research might be conducted. In addition to provisions authorizing the licensure of establishments, we have added other provisions which would require the registration of Recombinant DNA projects with the Secretary of HEW. In addition, as a basis for the entire regulatory scheme, we are suggesting that the Secretary of HEW be clearly authorized to promulgate standards for the conduct of Recombinant DNA research applicable to all firms and institutions, whether public or private. These same concepts were included in H.R. 4759 under the general heading of "Licensing Requirements". We feel that such provisions would be more appropriately designated as "Standards".

Our recommendations include specific provisions concerning:

I. Additional Findings
II. Standards
III. Licenses
IV. Registration of Research Projects
V. Inspections
VI. License Revocation
VII. Release of Proprietary Information

I. ADDITIONAL FINDINGS

(1) Recombinant DNA research offers great promise for the scientific application of new technology to many biological processes, including the treatment and prevention of various diseases;

(2) Responsible Recombinant DNA research should be encouraged;

(3) It is necessary that industry, government and academic scientists and institutions work together to achieve the potential benefits associated with Recombinant DNA research;

(4) The public interest will best be served by assuring that appropriate safeguards carefully take into account scientific freedom so that such research is encouraged, while at the same time recognizing that the health and welfare of the public as well as those engaged in the research must not be endangered;

(b) Such standards shall not be designed or construed to apply to genetic or other scientific experiments not involving the use of recombinant DNA.

(c) The Secretary shall periodically review regulations promulgated under subsection (a) and promulgate such amendments to such regulations as the Secretary determines to be necessary.

(d) For the purposes of this part, the term 'recombinant DNA' means molecules that consist of different segments of deoxyribonucleic acid which have been joined together in cell-free systems to infect and replicate in some host cell, either autonomously or on an integrated part of the host's genome.

IV. REGISTRATION OF RESEARCH PROJECTS

Any person who undertakes or is responsible for undertaking a project involving recombinant DNA shall register the project with the Secretary.

operator, or agent within thirty days of the completion of the inspection.

(c) No officer, employee, or agent designated by the Secretary to enter an establishment and conduct an inspection pursuant to this section shall be required to obtain a search warrant from any judicial officer prior to entering any establishment and conducting any inspection which is authorized by this section.

VII. RELEASE OF PROPRIETARY INFORMATION

Any information reported to or otherwise obtained by the Secretary or his representative pursuant to this Act which is exempt from disclosure pursuant to section 552 of Title 5, United States Code shall be considered confidential and shall not be disclosed. Upon a showing satisfactory to the Secretary by any person that any information, or portion thereof obtained under this Act by the Secretary or his representative either directly or indirectly from such person, would, if made public, divulge 1) trade secrets or 2) other proprietary information of such person, the Secretary or his representative shall not disclose such information and disclosure thereof shall be punishable under section 1905 of Title 18 U.S.C.

We support licensing and inspection of facilities, registration of research projects, and mandatory submission of reports. And, of course, we endorse the promulgation of regulations based on the existing NIH guidelines with whatever modifications may be necessary to make them applicable to all persons engaged in recombinant DNA research.

The use of institutional review committees or institutional biohazard committees, to approve and monitor DNA research is appropriate, in our view. Such committees have been used as a matter of routine in all of our research-based member firms for years. It is important to note in this regard that the drug industry has decades of expertise and experience in the safe handling of hazardous materials, including live viruses and bacteria, and is at least as sophisticated and perhaps more sophisticated in these procedures as any other element of the research community.

With many others, we believe that there should be a Federal preemption of State and local laws in order to assure the uniform enforcement of needed standards. Any proliferation of State or local laws and regulations could seriously impede the research which is necessary to determine the potential benefits and risks of the new breakthrough in technology. Elements of some or all of these provisions are contained in pending legislation and, in our opinion, offer a sound and reasonable basis for the regulation for recombinant DNA research which will assure the protection of the public and of the environment.

There are provisions in some of the pending bills which we cannot support. The restrictions on patents in S. 621 and H.R. 3592 are unnecessary and could work as a disservice to the public by discouraging research. We are generally opposed to specific limitations on the general patent laws such as those in section 6 of S. 621 and H.R. 3592 which would preclude the granting of a patent unless the NIH guidelines were strictly followed. The authority in the licensing and other provisions of pending legislation will prevent such problems. This section of the bills seems also to suggest substantially greater disclosure of information than ordinarily required in a patent application. We feel that demand for such disclosures would force or encourage scientists to avoid the patent system and rely on their common-law trade-secret protection.

These restrictions are therefore self-defeating and should be deleted from any bills now under consideration. These bills, S. 621 and H.R. 3592 would also impose strict liability on persons engaged in research and could very well cause the insurance industry to reassess its entire coverage for the drug industry and other industries. In the light of the responsible record of the drug industry in dealing with these and other potentially hazardous substances in research and production, we feel there is no justification for this requirement. One of the pending bills, H.R. 4759, would require that all P–4 and possibly P–3 research be confined to one of 10 centers to be designated by the Secretary of HEW. In our opinion, a requirement that P–4 research be limited to the first 10 centers approved by the Secretary is arbitrary and could limit this type of research exclusively to Government projects.

If industrial and academic laboratories satisfy statutory and regulatory requirements, we see no reason why they should be excluded

May 12, 1977

Hon. Ray Thornton, M. C.
Chairman, Committee on Science and Technology
U. S. House of Representatives
Washington, D. C. 20515

Dear Congressman Thornton:

During hearings before the Committee on Science and Technology on the subject of recombinant DNA research on April 28, 1977, you requested additional information on several points for purposes of the record.

I am pleased to provide the following information in compliance with your request which appears on pages 337 and 338 of the transcript.

1. A copy of the PMA publication entitled "Administrative Officers of the Member Firms and Associates of the Pharmaceutical Manufacturers Association".

2. PMA member firms directly engaged in recombinant DNA research in their own facilities include:

   a. Hoffmann-La Roche Inc.
   b. Eli Lilly and Company
   c. The Upjohn Company

3. PMA member firms supporting recombinant DNA research in academic institutions include:

   a. Abbott Laboratories
   b. Miles Laboratories
   c. SmithKline Corporation

4. The firm of Hoffmann-La Roche Inc. has announced plans for the construction of a P-4 facility. It is our understanding that such plans are being held in abeyance pending the outcome of proposed legislation.

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June, 1975

MEMBER FIRMS OF PMA

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064
(312) 688-6100

Alcon Laboratories, Inc.
P.O. Box 1959
Fort Worth, Texas 76101
(817) 293-0450

Allergan Pharmaceuticals
2525 Dupont Drive
Irvine, California 92664
(714) 833-8880

Alza Corporation
950 Page Mill Road
Palo Alto, California 94304
(415) 493-3200

Ames Company
Div. of Miles Laboratories, Inc.
1127 Myrtle Street
Elkhart, Indiana 46514
(219) 264-8111

Armour Pharmaceutical Company
Greyhound Tower
Phoenix, Arizona 85077
(602) 248-5230

Arnar-Stone Laboratories, Inc.
601 East Kensington Road
Mt. Prospect, Illinois 60056
(312) 255-0300

B.F. Ascher & Company, Inc.
5100 East 59th Street
Kansas City, Missouri 64130
(816) 363-5900

Astra Pharmaceutical Products, Inc.
Neponset Street
Worcester, Massachusetts 01606
(617) 852-6351

Ayerst Laboratories
Div. of Amer. Home Products Corp.
685 Third Avenue
New York, New York 10017
(212) 986-1000

J.T. Baker Chemical Company
222 Red School Lane
Philipsburg, New Jersey 08865
(201) 859-2151

Barnes-Hind Pharmaceuticals, Inc.
895 Kifer Road
Sunnyvale, California 94086
(408) 736-5462

Barry Laboratories, Inc.
461 N.E. 27th Street
Pompano Beach, Florida 33064
(305) 943-7722

Baxter Laboratories, Inc.
6301 Lincoln Road
Morton Grove, Illinois 60053
(312) 267-6900

Becton, Dickinson and Company
Rutherford, New Jersey 07070
(201) 939-9000

Beecham Laboratories
Div. of Beecham Inc.
501 Fifth Street
Bristol, Tennessee 37620
(615) 764-5141

BioQuest
P.O. Box 243
Cockeysville, Maryland 21030
(301) 666-0100

The Blue Line Chemical Company
302 South Broadway
St. Louis, Missouri 63102
(314) 421-0900

Bowman Pharmaceuticals
Div. of Bowman, Inc.
965 Cleveland Avenue, N.W.
Canton, Ohio 44702
(216) 456-2431

Breon Laboratories Inc.
90 Park Avenue
New York, New York 10016
(212) 972-5812

Flint Laboratories
Div. of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015
(312) 273-3680

E. Pougera & Co., Inc.
Cantiague Rock Road
Hicksville, New York 11802
(516) 681-1222

Hoechst-Roussell Pharmaceuticals
Incorporated
Route 202-206 North
Somerville, New Jersey 08876
(201) 685-2000

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110
(402) 464-6311

Hollister-Stier Laboratories
North 3525 Regal Street
Spokane, Washington 99207
(509) 489-5656

Hoyt Laboratories
Div. of Colgate-Palmolive Company
633 Highland Street
Needham, Massachusetts 02194
(617) 444-8610

Hyland Division
Travenol Laboratories, Inc.
P.O. Box 2214
Costa Mesa, California 92626
(714) 540-5000

Hynson, Westcott & Dunning, Inc.
1030 North Charles Street
Baltimore, Maryland 21201
(301) 837-0890

Inolex Corporation
2300 Prudential Plaza
Chicago, Illinois 60601
(312) 527-5410

Ivers-Lee
Div. of Becton, Dickinson & Company
147 Clinton Road
West Caldwell, New Jersey 07006
(201) 575-9000

Ives Laboratories, Inc.
685 Third Avenue
New York, New York 10017
(212) 986-1000

Johnson & Johnson
501 George Street
New Brunswick, New Jersey 08903
(201) 524-0400

Knoll Pharmaceutical Company
30 North Jefferson Road
Whippany, New Jersey 07981
(201) 887-8300

Kremers-Urban Company
P.O. Box 2038
Milwaukee, Wisconsin 53201
(414) 354-4300

Lafayette Pharmacal Inc.
522-26 North Earl Avenue
Lafayette, Indiana 47904
(317) 447-3129

Lakeside Laboratories, Inc.
1707 East North Avenue
Milwaukee, Wisconsin 52301
(414) 271-9400

Lederle Laboratories
Div. of American Cyanamid Company
Middletown Road
Pearl River, New York 10965
(914) 735-5000

Eli Lilly and Company
307 East McCarty Street
Indianapolis, Indiana 46206
(317) 636-2211

Mallard Inc.
3021 Wabash Avenue
Detroit, Michigan 48216
(313) 964-3910

Mallinckrodt, Inc.
3600 North Second Street
St. Louis, Missouri 63137
(314) 231-8980

Marion Laboratories, Inc.
10236 Bunker Ridge Road
Kansas City, Missouri 64137
(816) 761-2500

McGaw Laboratories
1015 Grandview Avenue
Glendale, California 91201
(213) 246-6521

McNeil Laboratories, Inc.
Camp Hill Road
Fort Washington, Pennsylvania 19034
(215) 836-4500

Sandoz Pharmaceuticals
Route 10
East Hanover, New Jersey 07936
(201) 386-1000

Savage Laboratories, Inc.
1000 Main Street
Missouri City, Texas 77459
(713) 499-4547

R.P. Scherer Corporation
9425 Grinnell Avenue
Detroit, Michigan 48213
(313) 571-6100

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
(201) 931-2000

Schering-Plough Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
(201) 931-2000

G.D. Searle & Co.
P.O. Box 1045
Skokie, Illinois 60076
(312) 982-7000

SmithKline Corporation
1500 Spring Garden Street
Philadelphia, Pennsylvania 19101
(215) 854-4000

Smith Kline & French Laboratories
1500 Spring Garden Street
Philadelphia, Pennsylvania 19101
(215) 854-4000

Smith, Miller & Patch
Div. of Cooper Laboratories, Inc.
1259 Route 46
Parsippany, New Jersey 07054
(201) 334-9800

E.R. Squibb & Sons, Inc.
P.O. Box 4000
Princeton, New Jersey 08540
(609) 921-4000

Standard Pharmacal Corporation
1300 Abbott Drive
Elgin, Illinois 60120
(312) 742-6622

Stuart Pharmaceuticals
Div. of ICI United States Inc.
P.O. Box 751
Wilmington, Delaware 19897
(302) 575-3000

Syntex Laboratories, Inc.
3401 Hillview Avenue
Palo Alto, California 94304
(415) 855-5050

Tenneco Chemicals, Inc.
Organics and Polymers Div.
Turner Place, P.O. Box 2
Piscataway, New Jersey 08854
(201) 981-5000

The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001
(616) 382-4000

USV Pharmaceutical Corporation
One Scarsdale Road
Tuckahoe, New York 10707
(914) 779-6300

The Vale Chemical Co., Inc.
1201 Liberty Street
Allentown, Pennsylvania 18102
(215) 433-7579

Walker, Corp. & Co., Inc.
P.O. Drawer 1320
Syracuse, New York 13201
(315) 463-4511

Wallace Laboratories
Div. of Carter-Wallace, Inc.
Half Acre Road
Cranbury, New Jersey 08512
(609) 655-1100

Wallerstein Company
Div. of Travenol Laboratories, Inc.
200 Wilmot Road
Deerfield, Illinois 60015
(312) 463-1220

Wampole Laboratories
Div. of Carter-Wallace, Inc.
35 Commerce Road
Stamford, Connecticut 06904
(203) 325-1591

Warner-Chilcott Laboratories
Div. of Warner-Lambert Company
201 Tabor Road
Morris Plains, New Jersey 07950
(201) 540-2000

Warren-Teed Pharmaceuticals Inc.
582 West Goodale Street
Columbus, Ohio 43215
(614) 221-5574

Mr. THORNTON. Fine.

And in connection with that, I wonder if you might identify the firms that you have described as being engaged in DNA recombinant molecule research and the level of risk that, to the best of your knowledge, those firms are engaged in.

I believe you said three are currently carrying out the research and that three others were planning to do so in the near future. Is there one that is planning a P–4 facility?

Dr. ADMS. Yes; to my knowledge there are plans for the facility, for a P–4 facility. Whether or not that construction has been undertaken at this point in time I cannot say, Congressman.

I know there were some second thoughts following the great amount of public controversy that arose.

Mr. THORNTON. I think it would be useful to our subcommittee to know who the firms are. Now that that relates to the general nature of the legislation but rather to the nature of the interest that is being expressed. It might give us some indication as to the character of the firms that are moving into this area. Such information as you can provide us, we would appreciate.

Dr. ADAMS. I would be pleased to provide that to you, sir.

Mr. THORNTON. And submit it, if you will, later for the record. I take it that you view the NIH guidelines as being adequate protection to the public, as those guidelines have now been formulated.

Do I also understand that you think some statutory enactment of those guidelines might be useful, or am I going beyond your testimony in that statement?

Dr. ADAMS. No. We endorse legislation and the promulgation of regulations thereunder basing those regulations on the existing NIH guidelines, with whatever modifications may be necessary so that they can apply and will apply to other than NIH-sponsored research.

Mr. THORNTON. What would be the effect of a State or local community establishing higher standards than those contained in a uniform Federal standard upon the private sector as to whether it would conduct such research? Would this have any effect as to your choice of locations where research would be conducted?

Dr. ADAMS. I assume that it would, Congressman, if a local community posed a ban or severe restrictions, standards higher than those which ultimately would be promulgated in guidelines, I think in order to continue the research and continue the endeavor they might consider a relocation of their research facility.

Mr. THORNTON. In that connection, it has been suggested in informal discussions that there might be a rationale for some variation in standards from location to location based upon a scientific analysis of the risk, the benefits, and so on, and that this could be made judgmentally rather than simply leaving that decision to an unreviewed local determination. Do you have any comments with regard to that?

Dr. ADAMS. Let me respond in this way. We would hope that the standards as promulgated, under whatever legislation finally passes at the Federal level, would be adequate to protect the public against what they deem to be or imagine to be the problems that may be created, and that there would be no need for enactment of local ordinances or laws to regulate this type of research.

Mr. BRENNAN. That is what we are suggesting.

Mr. BROWN. Mr. Chairman.

Mr. THORNTON. I would be pleased to yield to the gentleman from California, Mr. Brown.

Mr. BROWN. This issue raised some significant points.

I would have some problems with local jurisdictions seeking to regulate the nature of the biological or physical containment aspect of DNA research. I do not think they are generally competent. There are exceptions to this, of course. But on the other hand, the Supreme Court has upheld many times the right of local communities to prohibit such simple things as a house, in the *Petaluma* case, for example. If they do not want more houses in Petaluma, you can't build them there.

And, obviously, they would have even greater legal authority in the case of a facility such as a DNA research facility or something of that sort, but that has to be distinguished from regulating where that facility is built and the kind of protection that is built into it. Their practice is to say, yes or no, you cannot have it. And there may be some other aspects of this power that local agencies have. But I would want us to make some distinction here, because I would not want to infringe upon that right, just as I would not want them tinkering with something that the NIH had constructed in the way of good national regulations for the protection that ought to be built into one of those facilities.

Mr. THORNTON. I would like to comment and join in the expression of views made by my distinguished colleague from California.

It would seem to me that such rights of zoning and determination of the physical safety of structures might well be outside the area of regulation to which we are addressing ourselves. And perhaps I was ill-advised in using the example of a structure on an earthquake fault as an illustration of the kind of problem. But I was trying to get at the question of what method would be used to review a local decision relating to the conduct of DNA recombinant research?

Mr. BRENNAN. Mr. Thornton, I think that we, as I am sure this committee does, have a very serious concern about the potential intrusion of government bodies here into the basic research endeavor. We feel in this area that we are going a long way from our normal basic position on this subject in suggesting that there is a role that government can play in regulating basic research here. At the same time we are quite concerned that localities or local government agencies which just are not equipped to answer these questions about basic research and how to regulate it would make any number of mistakes which would be harmful to the overall research process and it is hard to factor out when you are taking about pipes and air ducts and when you are talking about the basic research project. So I guess that maybe we are talking about the same thing, that we think on the philosophical point of regulating the research project that there ought to be a central force in Federal Government which would clear the regulation of that, and on the other hand, the building or the air ducts and water could well be regulated in any manner at a local level.

Mr. THORNTON. Dr. Adams, I was slightly concerned that your statement seemed to be defensive against the possibility that PMA had made changes in its position. I would personally hope that the asso-

We use the 10-liter guidelines just as the current limit.

Dr. ADAMS. Mr. Hollenbeck, I have no idea. I have to assume from a brief conversation with some of our scientists that we are in the preliminary research stage at this point in time.

Mr. HOLLENBECK. And is there any guess or speculation as to what types of production or types of products you may be engaged in producing?

Dr. ADAMS. The technology has a wide application, not only in the drug industry but elsewhere. I can name several for you. This technique—and I think Dr. Johnson may testify on this later—could well be used as a means of producing insulin by fermentation rather than by extraction as is the present case. This would be terribly important as we detect more cases of diabetes not only in the United States but worldwide, because there is a finite number of hogs from which the pancreases are obtained to produce insulin. It has an important application there.

It might be exceedingly useful in producing a new species of organism that will produce better antibiotics. It would be exceedingly useful in producing a number of natural products, for example, some of the naturally occurring hormones and other products that at the moment have to be extracted, for example, the pituitary extract. The pituitary is about the size of the end of my little finger, and it does not yield much in the way of product and yet by this process you could find the gene that produces this and combine it in making large quantities for whatever utilization it may have in medicine. The application excites the imagination, because this does lend itself to many commercial processes in fermentation and it does result in larger yields than otherwise would be available.

Mr. BROWN. Would the gentleman yield on that point?

Mr. HOLLENBECK. Yes.

Mr. BROWN. One of the things that this committee has frequently mentioned as an area requiring additional research is the enhancement of the nitrogen fixation process.

Is it a possible area in which we might use recombination DNA research hopefully to find a new strain of bacteria that would process nitrogen fixation capabilities?

Dr. ADAMS. Congressman Brown, I am told that there is a distinct possibility.

It is in the field of agricultural chemistry and we are not here to represent them, but I am told that that is a very distinct possibility and it has been mentioned a number of times in many of the articles in scientific journals and elsewhere.

Mr. HOLLENBECK. There has been some mention of biohazard committees. Do the three firms which are currently carrying out DNA recombinant research now have such committees?

Dr. ADAMS. I cannot speak to that. I am confident that while they may not have a distinct biohazards committee, they certainly do have an institutional review committee that takes a look at the research protocol and I do not think it would be any great jump for them to make it an institutional biohazards committee to look at that as well.

Mr. HOLLENBECK. What is the association's position on, call it "public" representation on the biohazards committee?

Dr. ADAMS. Thank you, sir.

Mr. BROWN. On page 8 of your statement you refer to section 11 of the bill S. 1217. I do not have that in front of me, but I assume that it refers to some sort of discrimination against employees who report unfavorable conditions or something of that sort in the laboratory.

Dr. ADAMS. I will refer your question to Mr. Brennan.

Mr. BRENNAN. That portion of the Senate bill essentially provides that there shall be no discrimination against an employee who makes a statement or testifies or says something else which is offensive or injurious to his employer. In order to protect the employee, it gives him the right to come forward and say something of a derogatory nature to a regulatory body or otherwise without jeopardizing his employment.

Currently in the Occupational Safety and Health Act there is a similar provision. It directs the Secretary of Labor to make an investigation and if the complaint about discrimination is upheld, then the Secretary of Labor makes a finding and forwards that to the Department of Justice for the initiation of a court case for back pay or reinstatement of the employee if he has been fired.

That provision of S. 1217 would give the Secretary of Labor the authority on the spot to make the back pay determination or whatever other—assess the penalty and then there would be a right for the employer to go to the court of appeals to determine whether or not the Secretary of Labor's decision was arbitrary and capricious or otherwise unfair.

So, essentially what we are saying is that we do not mind the provision on discrimination against employees as long as you follow what is in the current Occupational Safety and Health Act and make the Secretary of Labor go to court about it rather than make his own determination.

Mr. BROWN. It seems to me quite reasonable to expect that we have, as nearly as possible, one standard set of procedures under those various acts to handle that kind of problem.

Mr. BRENNAN. We do not see the necessity in recombinant DNA research to change what was covered under the Occupational Safety and Health Act.

Mr. BROWN. You raise a much more important problem, I think, Dr. Adams, when you bring up the question of liability. This is an increasingly significant problem, particularly concerning the health profession in general. I guess malpractice suits can be included in this general category of problems, and this has received a great deal of attention. But we have this situation in connection with the swine flu legislation where the legislation was held up until an adequate provision for liability was incorporated in it. Of course we have similar problems with nuclear situations, where under the Price-Anderson Act, which has the Government assume certain liabilities above a certain limit in order to protect the public. It limits the liability of the private industry, is what it amounts to. Do you anticipate that this kind of a problem is going to be a serious one in this research and development?

Dr. ADAMS. I am going to ask Mr. Brennan to respond to your question on liability. I think the concept of strict liability in a research endeavor would be a disincentive for research, I suspect because of the

results are the same as far as we are concerned. If the liability is substantially expanded, either because of the number of people involved or a change to strict liability, we are quite concerned that we just would not be insured in this type of research. And we do not see the concern there.

Just prior to our testimony in the Senate, Senator Bumpers, who I think first introduced this idea, testified about his bill before Senator Kennedy's committee. And he said that he really had introduced that in order to assure compliance with the standards. They are tied together, if you do not comply with the NIH standards then you are accountable under strict liability. He said if the ultimate legislation would assure that everyone would comply with the standards, he was not interested in that strict liability business and would take it off.

Mr. THORNTON. Thank you, Mr. Brown.

Let me amplify upon the last statement very briefly. The Senator's views are held in order to obtain compliance with the standards. Both the suggestion of strict liability and also the patent provisions, which would prohibit a patent from being issued unless there was strict compliance with NIH standards, were looked upon as being a means of insuring compliance with the standards. Is that also your impression?

Mr. BRENNAN. That is right, Congressman. And as I understand what Senator Bumpers was saying a couple of weeks ago in the Senate in his testimony, it was that—and we agree with this—if a licensure provision, as was written into the other Senate bill, was enacted, then there would seem to be no need for the kind of restrictions that he was talking about.

Mr. THORNTON. He is very strongly in favor of imposing standards?

Mr. BRENNAN. Yes.

Mr. THORNTON. Mr. Dornan.

Mr. DORNAN. The House has just gone into business so we may not have too much time before a quorum call on the vote.

On the Republican side we are supposed to be a bit more inclined, though not as a general rule, toward a free market platform. I ran on a platform against Government regulation at just about every level.

To be honest with you, with regard to the pharmaceutical industry, I feel inclined toward severe Government regulations, and this is because of some facts that I gleaned as the host of a television talk show over a period of more than a decade.

Some of the statement runs like this, that the drug industry in the United States and throughout the world—and may I ask if you represent also Roche Laboratories?

Mr. BRENNAN. We represent their U.S. business, yes.

Mr. DORNAN. That throughout the Western world, and the United States in particular, the drug industry produces three times the amount of pills that is necessary for the medical profession to prescribe, Point 1.

Point 2, the medical profession prescribes double the amount of pills that is necessary, particularly tranquilizers to women, and there are now nearly as many men on valium, Meprobamate, Librium, Quaalude or you name it, as there were women on these pills.

Mr. DORNAN. Gentlemen, because we do have a vote coming up, let me close this way. Every Congressman wants to think he is open-minded. We are the people who unleash the regulators on this country. I think the United States is being regulated to death, and it is destroying the market. I do not look for conspiracy or for any industry to lie really blatantly to Congressmen or to consumers. Could you furnish me the information on some of these points I have made, so that I can, with an open mind, evaluate some of the serious decisions we are going to have to make? The most serious among them, I believe, will be licensing firms, laboratories, generically, rather than licensing each specific project.

There are very few Congressmen that have, say, the scientific knowledge of Congressman Brown. Could you furnish me the overproduction statistics as your industry sees it and some comments on whether or not doctors, particularly in the field of tranquilizers, are being lax to the point of negligence in prescribing pills? I'll make a subcomment to my statement that it appears that women are being treated in a very chauvinist way. They get kicked out of the office with a pill prescription, whereas a man is told, "Henry, pull yourself together, get a grip on yourself." Could you also comment on this whole area of drugs coming into this country through covert sources, the Mexican warehouses? If you could get me some information and background on that, I'd appreciate it. I remember vividly Howard K. Smith announced over ABC that valium and meprobamate had been put on the dangerous substances list. I could only concur wholeheartedly in that, because I know that one community that I have some familiarity with, the Hollywood motion picture community, is totally "pilled" out of its mind. Tranquilizers are such a joke, that Hollywood's No. 1 producer, Norman Lear, wrote a scene in one of America's highest rated television shows, a kidnaping scene, where the police officer turns around to the crowd and asks "Does anyone have a valium" and the firemen on the scene, the police, the newsboys, the shoeshine boy, everyone in the crowd reached into his pocket and came up instantly with a valium pill. It is a big joke.

I do not think it is funny, because I know some people whose lives are being destroyed by tranquilizers.

So, could you give me some information so that I can approach this subject of DNA research to assure that the pharmaceutical companies in the years to come will not be the most regulated industry?

Dr. ADAMS. We will attempt to provide that information for you, Congressman.

I would like to correct one thing in the record. You used a term "dangerous for valium." All drugs are dangerous. It is a controlled drug.

Mr. DORNAN. Those would have been the words that Howard K. Smith used on that show. That was a year or two ago.

Dr. ADAMS. It is a controlled substance, and it is now scheduled, valium and meprobamate.

Mr. BRENNAN. He might have just said what you said, dangerous. But Dr. Adams is saying that it not the term of art.

Dr. ADAMS. It is not the term of art, it is a controlled substance and it is scheduled.

Director, Research (1972–73); Vice President, Research, Lilly Research Laboratories (1973–).

Military service: Active duty, U.S. Navy, Pacific Theater and Continental U.S. Enlisted as apprentice seaman; terminal rank, Lieutenant, USNR, 1943–46.

Professional societies: American Association for the Advancement of Science, American Association for Caucer Research, American Society for Cell Biology, Environmental Mutagen Society, International Society for Chemotherapy, Kansas Academy of Science, New York Academy of Science, Phi Sigma, Sigma XI, Society for Experimental Biology and Medicine.

Honors and areas of community interest: Nominee for one of the "Nation's Ten Outstanding Young Men" awards for 1960 by the United States Junior Chamber of Commerce. Member of a nine-man U.S. delegation to the United States-Japanese Conference on Leukemia, sponsored by the National Science Foundation as part of government to government scientific exchange program, Nagoya, Japan (1966).

Member of the Editorial Board of *Chemico-Biological Interactions* (1968–73). Member of Education Committee of Indianapolis Urban League (1968). President of Arlington High School Chapter of American Field Service Student Exchange Program (1969–70). Member of Curriculum Committee—Program for Continuing Biological Study—A national program sponsored by the AIBS. First program initiated at Western Michigan University, Kalamazoo, Michigan (1970). Member of the Edtorial Advisory Board of *Cancer Research* (1971–73). Associate Editor of *Cancer Research* (1974–). Member of Consultant Panel for National Cancer Program (1971). Member of Professional Education Committee, American Cancer Society, Indiana Branch (1972). Listed in *American Men of Science, World Who's Who in Science,* and *Dictionary of International Biography.*

Research interests and experience: Joined the Lilly research staff in 1953 in a program designed to ntilize tissue culture techniques in cancer research. Briefly assigned to developmental problems with mass production and safety testing of Salk polio vaccine, and then returned to cancer research. During the remainder of tbis period was actively involved in a variety of research interests. These included cancer chemotherapy, viral chemotherapy, viral oncogenesis, viral oncolysis, transduction in mammalian systems, comparative metabolism of cells of malignant and non-malignant origin, *in vitro* endocrine studies, tissue culture technology, and immunosuppression studies.

Currently, administratively responsible for senior investigators in broad area of biological research including the areas mentioned above, as well as pharmacology, endocrinology, physiology, biochemistry and drug metabolism.

Publications: He has published some 60 research papers in fields ranging from cancer chemotherapy and virology to heart cell function and the tissne-culture production of insulin.

JOHN M. HOLT

Title: Secretary and General Counsel, Pharmaceutical Division, Eli Lilly and Company.

Employed by Eli Lilly and Company: 1952.

Areas of Responsibility: Regulatory and legislative matters associated with pharmaceutical products.

Edncation: DePanw University, B.A., 1950; Indiana University School of Law, J.D., 1956.

Member: Indianapolis, Indiana, and American Bar Associations.

STATEMENT OF IRVING S. JOHNSON, VICE PRESIDENT OF RESEARCH, LILLY RESEARCH LABORATORIES, ACCOMPANIED BY JOHN M. HOLT, SECRETARY AND GENERAL COUNSEL

Dr. JOHNSON. Thank you very much. I appreciate your courtesy in permitting us to appear and have an opportunity to offer our comments.

I am Dr. Irving S. Johnson, vice president of research, Lilly Research Laboratories. I have administrative responsibility at Lilly for all preclinical biological research directed toward pharmaceutical products for human medicine, including Lilly's work to date in recombinant DNA research. Accompanying me is Mr. John M. Holt,

I might add, Mr. Chairman, that inserting a piece of foreign DNA in such an organism is not a far step from chemically modifying the existing DNA, and to a degree this technique can be viewed as an extension of the procedure which has been going on for many, many years.

It is also possible that DNA recombinations may produce hormones and other medically useful proteins. The biosyntheis of insulin which has been mentioned several times before this committee, is one possibility. In some instances, we may be able to produce significant quantities of materials as a contingency measure to prevent future shortages. In other instances, we may obtain therapeutic agents which are commercially nonexistent today.

I think Dr. Adams referred to human growth hormone as one of these possibilities, Interferon, factor 8 and antibodies are examples, and there are many others that can be suggested.

Concurrent with these programs, Lilly scientists have closely followed both the technical developments and those considerations which have led to public concern regarding the utilization of recombinant DNA techniques. We watched with great interest the plans for the Asilomar Conference and would have been happy to participate in discussions at that meeting.

In fact, I tried to do so. Industry was not represented at the Asilomar although industry possesses a great reservoir of technical skills relating to fermentation processes, biologic containment and infectious diseases. Industrial research scientists could have made substantive contributions.

It is my personal opinion that some of these considerations might have modified some of the approaches taken at Asilomar.

Mr. THORNTON. May I ask how you sought to participate at that meeting?

Dr. JOHNSON. I am not sure I did it correctly, Mr. Chairman.

I knew one of the organizing members of the committee personally and I called him by phone and asked him if we could participate. I do not know who he talked to or who he consulted with. He called me back and indicated that he thought that the thing had been so well formalized that there really was not any opportunity at that date.

Mr. THORNTON. There was no letter or formal rejection, just an informal comment?

Dr. JOHNSON. No; there was not.

We have also observed the development of the National Institutes of Health guidelines and we followed the guidelines on a voluntary basis in our research activities. In large measure, we endorse the guidelines but feel they could be improved from the standpoint of protection of proprietary information as I will note later in my comments to you.

Lilly has also shared its interest and the fact that is engaged in recombinant DNA research with its employees, its shareholders and the local community through interviews covered by newspapers, television, radio and national magazines.

I think that we have provided you and your staff with some of the examples of these, and I will not burden the record with their insertion.

I have personally arranged on at least two occasions for television cameras to come into our laboratory where this type of research is

What we demonstrated was that there was no difference in antibiotic sensitivity among these four strains. There was a 10,000-fold difference at the extremes in their pathogenicity for mice. My point is that we were able to measure pathogenicity and able to analyze it. We do this sort of thing routinely, and further demonstrated that E. coli, the organism which gets a lot of criticism in this area, has been used safely for pilot scale production and fermentation of therapeutic materials. This is equally true of the other organism, pseudomonas.

Have I answered your question, Mr. Chairman?

Mr. THORNTON. Yes, sir.

Thank you.

Dr. JOHNSON. Organisms producing toxins have long been used in the field of immunizing biologicals. Although individual accidents may have occurred, significant health hazards have not resulted from this work.

(2) The concept of insertion of "foreign" DNA causing antibiotic resistance has been raised. This has been discussed. This concern indicates a lack of knowledge of the mechanism of antibiotic action and the development of resistance. Almost all antibiotic agents act by interfering with cell wall synthesis at some step. If the organism produced through recombinant DNA technology can still make a cell wall, it should theoretically still be sensitive to some agent. If it cannot make a cell wall, it will not be a viable organism; that is, it will not continue to live and reproduce.

I might also point out that the mechanism of an antibiotic resistance is essentially the development and synthesis by the microorganism of enzymes to bio-degrade the antibiotic. It has evolutionary significance to the bacteria. Bacteria have been isolated from the so-called virgin antibiotic areas, in the middle of New Guinea, for example, where antibiotics have never been used. They even then had the ability to degrade penicillin and other antibiotics. But for no other species is the ability to degrade an antibiotic of any evolutionary significance, and it has never been demonstrated. I think the possibility of insertion of a piece of DNA from a cow or fruit fly or what-have-you in order to induce that mechanism of resistance is very unlikely.

(3) Much of the recombinant DNA laboratory work contemplated will be done with organisms of the type described by Dr. Curtis of the University of Alabama in his testimony before this committee. These organisms have been engineered to assure biological containment; that is, they will "self-destruct" if for some reason they are separated from the laboratory environment. In addition, other organisms are being considered by the NIH for certification which have an even higher safety factor.

(4) Doner DNA used in the work we have been engaged in at Lilly involves organisms which do not produce disease in man, such as streptomycetes.

(5) Work with certain disease-causing agents has been forbidden by the guidelines and we feel that these guidelines have been followed by the scientific community and certainly have been followed by us. There appear to be no practical benefits or medical reason to work with organisms in those categories prohibited by the guidelines.

hazards committee. The legislation should also provide for inspection of facilities, for reporting requirements, and as I have already noted for the protection of confidential data.

COMMENT ON ADVISORY COMMITTEE

Mr. Chairman, although we did not mention an advisory committee in our statement, we feel that any Federal legislation should provide specifically for a National Advisory Committee to assist the Secretary of HEW in matters involving recombinant DNA policies. Such a committee should include individuals from the public, from Government service, academic institutions, private industry, and agriculture. Their background and experience should include public health, industrial research, biochemical engineering, agriculture that is persons experienced in plant and animal genetics, as well as representatiou from the field of economics and law. Probably one-third of the group should be scientists who by training and experience have knowledge of recombinant DNA research techniques.

I might say that I have no problem with the lay public understanding of recombinant DNA technology from the conceptual viewpoint. I think where they may have difficulty is in the quantification of some of the problems associated with this technology.

In our view, the results of recombinant DNA research should not be subject to special patent restrictions. It is our understanding that the committee will examine patent questions associated with this work at a later date, and we will forward comments to the committee in conjunction with that hearing.

In that regard, Mr. Chairman, my legal associates have called my attention to House bill 6249 submitted by yourself and Mr. Teague in regard to comprehensive Government patent policy where you recognize clearly, I think, from the statements in that bill that patents are a stimulus to research and a contribution to the public welfare.

Mr. THORNTON. That is certainly the reason that patents were mention in the Constitution of the United States. The thought that by providing an opportunity for innovators to reap a reward from the invention, was considered to be important enough to be included in the Constitution. And our Federal Constitution does not, I think, merit any inattention.

Dr. JOHNSON. I agree completely.

I hope the foregoing comments have been of assistance to the committee and I will be glad to respond to any questions.

[The attachments to the statement follow :]

Mr. Chairman and Members of the Committee, I am Irving S. Johnson, Vice President of Research, Lilly Research Laboratories. I have administrative responsibility at Lilly for all preclinical biological research directed toward pharmaceutical products for human medicine, including Lilly's work to date in recombinant DNA research. Accompanying me is Mr. John M. Holt, Secretary and General Counsel of the company's Pharmaceutical Division.

Lilly has been engaged in the research, development, distribution, and production of pharmaceutical products for many years and of agricultural and cosmetic products for a number of years. The company has a strong commitment to research and has at present in excess of twenty-six hundred scientists and technicians involved in its research programs. Their activities have made possible a wide variety of products which have benefited both human health and agriculture.

Lilly supports the enactment of legislation to provide appropriate public health and environmental safeguards for recombinant DNA research. In this regard, Lilly endorses the views of the Pharmaceutical Manufacturers Association as expressed by Dr. Adams and Mr. Brennan in the Association's testimony today.

Our purpose in appearing is not to provide a commentary on recombinant DNA research technology. The Committee has had excellent testimony from Dr. Maxine Singer and others on recombinant techniques. We will comment briefly on Lilly activities in the recombinant DNA research field; the nature of industrial

Concurrent with these programs, Lilly scientists have closely followed both the technical developments and those considerations which have led to public concern regarding the utilization of recombinant DNA techniques. We watched with great interest the plans for The Asilomar Conference and would have been happy to participate in discussions at that meeting. Industry was not represented at the Asilomar although industry possesses a great reservoir of technical skills relating to fermentation processes, biologic containment and infectious diseases. Industrial research scientists could have made substantive contributions.

We have also observed the development of the National Institutes of Health guidelines, and we followed the guidelines on a voluntary basis in our research activities. In large measure, we endorse the guidelines but feel they could be improved from the standpoint of protection of proprietary information as noted later in these comments.

Lilly has also shared its interest and the fact that it is engaged in recombinant DNA research with its employees, its shareholders and the local community through interviews covered by newspapers, television, radio and national magazines. In addition to these interviews, I have personally arranged for television viewing of our laboratories on several occasions. I participated in the recent public discussions conducted by the National Academy of Sciences on recombinant DNA technology. We might also note that in May of 1976, Lilly convened an international symposium on the possibility of utilizing recombinant

pathogenic for man have been used in the fermentation of therapeutic agents on a production scale. Organisms producing toxins have long been used in the field of immunizing biologicals. Although individual accidents may have occurred, significant health hazards have not resulted from this work.

(2) The concept of insertion of "foreign" DNA causing antibiotic resistance has been raised. This concern indicates a lack of knowledge of the mechanism of antibiotic action and the development of resistance. Almost all antibiotic agents act by interfering with cell wall synthesis at some step. If the organism produced through recombinant DNA technology can still make a cell wall, it should still be theoretically sensitive to some agent. If it cannot make a cell wall, it will not be a viable organism; that is, it will not continue to live and reproduce.

(3) Much of the recombinant DNA laboratory work contemplated will be done with organisms of the type described by Dr. Curtis of the University of Alabama in his testimony before this Committee. These organisms have been engineered to assure biological containment; that is, they will "self-destruct" if for some reason they are separated from the laboratory environment. In addition, other organisms are being considered by the NIH for certification which have an even higher safety factor.

The possibility of premature disclosure of research programs and accomplishments with a possible loss of patent rights in the U.S. and abroad will discourage industrial commitment to the new recombinant DNA technology.

In an organization such as our laboratories, incentives are important to encourage participation in research programs at that point in time when new technology develops.

For example, Lilly's early involvement in tissue culture permitted its participation in the development of poliomyelitis vaccine. Other examples could be cited.

We trust that the Congress will carefully evaluate the need for confidential treatment of proprietary information resulting from private research activity. We might note that the Inter-agency Task Force considering recombinant DNA legislation also recommended that proprietary data be protected.

Pending Federal Legislation

As noted earlier in this statement, Lilly supports the enactment of a federal statute in this field. We feel such an act should place the regulation of recombinant DNA research under the Department of Health, Education, and Welfare. The act should provide for licensure of all facilities engaged in recombinant DNA research with appropriate authority for exemptions from licensure requirements for those activities that do not involve public health or environmental hazards. Consistent with the

LILLY IS

. . . RESEARCH AND DEVELOPMENT

Most of the products, including the most important ones, offered by the company today have resulted from its extensive research and development program.

Worldwide research in the life sciences is conducted by the Lilly Research Laboratories, a division of the company.

This research is concerned primarily with the discovery or identification of synthetic chemicals and natural products and their effects on living organisms—human, plant, and animal.

Efforts are directed toward the discovery of products to prevent and treat diseases in human beings and animals and to increase the efficiency of plant and animal food production as well as to improve the quality of cosmetic preparations.

Research efforts stress the study of plant hormones and agents to affect the growth and health of plants and encompass research relating to skin care and treatment.

In the search for compounds that will cure or alleviate diseases, special emphasis is placed on cancer, infectious diseases, parasitic diseases, and diseases of the endocrine, cardiovascular, nervous, and gastrointestinal systems.

Research relating to human health can also be applicable to animal health problems, as in the case of agents to cure infectious diseases.

In the agricultural sciences, research personnel are working in the areas of plant physiology and disease control, animal nutrition and reproduction, and veterinary medicine.

The ultimate aim of research and development projects is improving the quality of living by preventing or combating illness, reducing the time and thus the cost of hospital care, and helping increase the world supply of food and fiber.

In addition to research activities in Lilly laboratories, the company sponsors and underwrites the cost of research by independent organizations and contracts with others for the performance of research in their facilities.

May, 1978

The safety and effectiveness of new products are established through clinical evidence gathered from physicians, hospitals, medical schools, and other research organizations in this country and numerous other countries.

Research Personnel

Approximately 2,475 people, including a substantial number who are physicians and scientists holding graduate or postgraduate degrees and highly skilled technical personnel, are engaged in research and development activities.

One of the many indications of the impact of these men and women is their contribution to the world reservoir of scientific knowledge through the presentation of 320 scientific papers, on an average, annually.

Research and Development Expenditures

In the past 10 years, $660.7 million has been spent on research and development by Eli Lilly and Company. In 1975 alone, the company expended approximately $104.3 million.

These annual expenditures averaged approximately 9 percent of the company's consolidated net sales in the last five years.

Major Research Facilities

Lilly Research Laboratories and the Lilly Laboratory for Clinical Research at William N. Wishard Memorial Hospital, both in Indianapolis

Greenfield (Ind.) Laboratories

Lilly Research Centre Limited, at Windlesham, England

Agricultural field research stations located throughout the United States and abroad

Research Accomplishments

Major successes and achievements of Lilly research and development in the past half-century include:

to produce a long-acting penicillin, Lilly scientists discovered procaine penicillin G. It combined ease of administration and relative freedom from pain with prolonged action.

1952 Ilotycin®—More than one hundred thousand fungi were isolated from soil samples and tested in Lilly laboratories before this wide-spectrum antibiotic was found.

1954 Synthesis of Lysergic Acid—At a time when there was a worldwide shortage of natural ergot alkaloids, which are essential in obstetrics, Lilly organic chemists succeeded in synthesizing lysergic acid, a basic compound in the structure of these alkaloids. Chemists had been trying to achieve this feat for more than thirty-five years.

1955 Salk Poliomyelitis Vaccine—As early as the late 1940's Lilly scientists had begun to investigate the then-new field of tissue culture, the technique of growing animal tissue cells in a nutrient chemical solution. This experience in tissue culture later enabled the Lilly company to play a leading role in mass-producing poliomyelitis vaccine. Between the year preceding the vaccine's introduction and 1969, the number of reported cases of paralytic polio in the United States declined from 18,308 to 20.

V-Cillin®—An oral penicillin stable in stomach acids, penicillin V, was introduced under the trademark V-Cillin®. It rapidly achieves therapeutic concentrations in the blood that are significantly higher than those produced by equal amounts of oral penicillin G.

1956 Glucagon—Among the scientific "firsts" achieved by Lilly researchers was the purification, crystallization, and chemical structure determination of a pancreatic hormone called "glucagon." This basic research program also established the usefulness of glucagon in treating patients who suffer symptoms because of low blood sugar. Glucagon was marketed in 1960.

1957 Darvon®—A nine-year search culminated in the introduction of Darvon, a widely accepted prescription drug for alleviation of mild to moderate pain.

Hygromix®—The feed additive Hygromix contains hygromycin and is used in controlling intestinal worms in both poultry and swine. It was the first worm-control agent that could be fed continuously.

Rabies Vaccine—A safer rabies vaccine, produced in embryonated duck eggs, was discovered by Lilly scientists. It was the first commercially available vaccine for human use for which the rabies virus was grown in nonnervous tissue. As a consequence, it is virtually free of the "paralytic factor" that sometimes causes paralysis and death during treatment with conventional rabies vaccines.

Structure of Erythromycin—The structure of erythromycin, one of the first of a new class of antibiotics known as the "macrolides," was determined.

1958 Ilosone®—A derivative of erythromycin, this oral antibiotic provides dependable absorption.

Vancocin® HCl—A Lilly-discovered antibiotic, Vancocin HCl was introduced to combat resistant strains of *Staphylococcus aureus*. It is frequently lifesaving in patients whose infections are resistant to other antibiotics.

Dichloroisoproterenol—The first beta-adrenergic blocking agent was discovered. It has led to the development in other laboratories of related compounds that are *useful in managing heart diseases, including* angina pectoris.

1960 Brevital® Sodium—The company's continued interest in the barbiturates led to the introduction of this potent, injectable, barbiturate anesthetic agent of extremely short duration of action. It has come to be widely used in short surgical procedures, including dental surgery.

1961 Velban®—Eli Lilly and Company, which had been engaged in fundamental cancer studies for more than four decades, introduced two new weapons in the fight against cancer. The first was Velban, an alkaloid derived from the periwinkle, for the treatment of generalized Hodgkin's disease and a rare type of malignancy called choriocarcinoma. It marked the first time that an alkaloid from a plant was used in cancer therapy.

1962 Tylan®—The antibiotic Tylan was discovered by Lilly scientists and introduced for use exclusively in animals. It aids in the control of respiratory disease in poultry.

1975 Nebcin®—Nebcin, used in the treatment of a broad range of infections, was introduced in the United States.

Rumensin®—The company began marketing Rumensin for use in feedlot cattle, as a product to increase feed efficiency.

1976 Nalfon®—Nalfon is a nonsteriodal, anti-inflammatory compound indicated for relief of the signs and symptoms of rheumatoid arthritis and in the long-term management of the disease.

Amytal® (amobarbital, Lilly)
Amytal® Sodium (sodium amobarbital, Lilly)
Aventyl® HCl (nortriptyline hydrochloride, Lilly)
Balan® (benefin, Elanco)
Brevital® Sodium (sodium methohexital, Lilly)
Coban® (monensin sodium, Elanco)
Cordran® (flurandrenolide, Dista)
Darvon® (propoxyphene hydrochloride, Lilly)
Dolophine® Hydrochloride (methadone hydrochloride, Lilly)
Drolban® (dromostanolone propionate, Lilly)
Duracillin® A.S. (sterile procaine penicillin G suspension, Lilly)
Dymelor® (acetohexamide, Lilly)
Dymid® (diphenamid, Elanco)
Ergotrate® Maleate (ergonovine maleate, Lilly)
Hygromix® (hygromycin B, Elanco)
Iletin® (insulin, Lilly)
Ilosone® (erythromycin estolate, Dista)
Ilotycin® (erythromycin, Dista)
Keflex® (cephalexin, Lilly)
Keflin® (cephalothin sodium, Lilly)
Kefzol® (cefazolin sodium, Lilly)
Merthiolate® (thimerosal, Lilly)
Metycaine® Hydrochloride (piperocaine hydrochloride, Lilly)
Nalfon® (fenoprofen calcium, Dista)
Nebcin® (tobramycin sulfate, Lilly)
Oncovin® (vincristine sulfate, Lilly)
Paarlan® (isopropalin, Elanco)
Protamine, Zinc & Iletin® (protamine zinc insulin suspension, Lilly)
Rumensin® (monensin sodium, Elanco)
Seconal® (secobarbital, Lilly)
Spike® (tebuthiuron, Elanco)
Surflan® (oryzalin, Elanco)
Treflan® (trifluralin, Elanco)
Tylan® (tylosin, Elanco)
Vancocin® HCl (vancomycin hydrochloride, Lilly)
V-Cillin® (phenoxymethyl penicillin, Lilly)
Velban® (vinblastine sulfate, Lilly)

PHARMACEUTICAL MANUFACTURERS Association

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WASHINGTON, D.C. 20005
AREA CODE 202 296 [illegible]

C. JOSEPH STETLER
PRESIDENT

September 29, 1976

Donald S. Fredrickson, M. D.
Director
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Fredrickson:

We appreciate the opportunity to provide our views and comments on the patent policy considerations regarding DNA research raised in your September 7, 1976 letter.

The scientific, moral and social responsibilities of the scientific community in the new field of recombinant DNA research and development have been the subject of much discussion in recent months. I know that you are generally familiar with the PMA's September 22, 1976 testimony before the Senate Labor and Public Welfare Committee on this subject. Enclosed is a copy of our statement in which the PMA notes its support of the general approach of the June 23, 1976 National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules." The pharmaceutical industry supports the concept of these voluntary guidelines, subject to minor modifications. The research-based drug industry will undoubtedly have few problems in achieving full compliance with the spirit of the guidelines.

The PMA, and its member companies, also strongly support the present system of laws in the United States for protecting intellectual property rights. The United States patent law is an essential aspect of intellectual property right protection in this country, and we oppose any attempts to weaken this system to the detriment of both the public and the research and development community. Our support of the United States patent laws in providing an effective incentive to conduct research and to develop research results to commercial applications encompasses both Government and privately funded efforts.

which comply with appropriate Governmental guidelines on DNA research. It would be objectionable for the Department to "approve" particular licensees to to "approve" specific terms or conditions in any licensing agreements with particular licenseea.

As to those Government-funded institutions which do not operate under an IPA, the Department should condition the granting of ownership to identified inventions on the institution's willingness to (1) abide by Governmental guidelines and (2) license only those concerns which also comply with these guidelines.

Again, we appreciate the opportunity to comment on this very important aspect of DNA research activities. We will be pleased to discuss with you in greater detail our recommendations of this area if you have any further questions.

Respectfully submitted,

C. Joseph Stetler

Enclosure

Industry scientists immediately recognized the potential applications of this new technology to many biological processes, particularly in the fields of medicine and agriculture, and more specifically in the production of important drugs from natural sources. It is also well recognized by scientists in the drug industry and elsewhere that there are potential risks inherent in this new technology and that great caution must be exercised in seeking its benefits for mankind. We believe the drug industry has the proven scientific experience and capability to exercise that judgment.

Recombinant DNA research has been, and will continue to be, the subject of much debate on the question of balancing scientific freedom to pursue new avenues of research on the one hand, and the need for peer review and compliance with voluntary controls on the other. We believe that these two concepts are compatible and are accepted by responsible scientists and management in the drug industry and by other elements of the scientific community. To this end, it is our opinion that a good start has been made in the "Guidelines for Research Involving Recombinant DNA Molecules", published in the Federal Register on July 7 by the National Institutes of Health.

As you may be aware, representatives of the drug industry took part in a meeting called by the Director of NIH on June 2 of this year. On that occasion, as the PMA spokesman, I said that our member firms would respond to the request for critical review of the guidelines and that immediate steps would be taken to convene a panel of experts for that purpose. That panel has since studied the question and, in addition, we have requested comments from all of our member firms for submission to the Director of the National Institutes of Health by the due date of November 1.

We commend the NIH for establishing guidelines and, particularly, for its efforts in seeking a consensus within the scientific community and from the public and private sectors. Research in this field holds great promise, and it is fair to expect that the same innovative genius which led to its discovery can also design systems to control it through peer review and physical and biological containment.

It is important to note that the drug industry is one of the most sophisticated scientific institutions engaged in the handling of biohazardous materials. Some PMA member firms have long experience in working with pathogenic bacteria, viruses, rickettsial and other pathogenic microbiological organisms. For example, the entire technology of vaccine research and production requires intimate knowledge of bacterial and viral genetics and is based on rigid adherence to appropriate levels of physical and biological containment.

Another example -- the use of drug-resistant organisms to test new antibiotics and other chemotherapeutic agents against these strains of pathogenic microorganisms. Such research has led to the discovery of important new medicines. It has not resulted in any public health problems.

There is little doubt then that the drug industry will be able to meet appropriate standards for physical and biological containment levels of recombinant DNA research and development. In fact, a fail-safe system and a favorable benefit-risk ratio have already been established.

The PMA Expert Advisory Committee, which was convened in July agrees that the spirit and intent of the NIH guidelines are quite acceptable. The panel further agrees that with some minor modifications, pharmaceutical firms would have few problems in applying the guidelines to their own research programs. Based on responses to date to our request for comments and subject to these minor modifications which do not involve elements of risk or safety, it is fair to assume that PMA member firms will voluntarily comply with the guidelines.

In no instance was there any indication by our panel that the guidelines were inadequate to provide the necessary and desirable safeguards. Nor were there any reservations about industry's ability to comply with the proposed containment levels. It was also the consensus of the panel that the creation of recombinant DNA biohazard and/or research committees to review and approve research projects would pose no serious problem to industry and could be quickly implemented. Review of the records of the meetings of such committees present no serious difficulty, except insofar as such minutes might involve proprietary or trade secret information. Such records should not necessarily be made public, but they could be made available to appropriate authorities where confidentiality could be guaranteed. We do not view those features of the guidelines which might impinge on such intellectual property rights as insurmountable and trust that satisfactory modifications to the guidelines could be achieved.

The only other major concern of industry would be the restriction on volumes of greater than ten liters. Such a restriction would be unrealistic in any scale-up operation for production purposes. We recognize that the guidelines are primarily directed to small-scale research but provision must be made for commercial application as technology expands and the state of the art changes. As in the case of trade secrets and proprietary rights, we believe modifications or exceptions can accommodate this concern.

The particular provisions of the Guidelines which impact on intellectual property rights and volume restrictions are those which impose formalized approval and reporting requirements on the principal investigator as outlined in the chapter entitled "Roles and Responsibilities" FR (41) 131 on page 27920, and related portions of the Guidelines. We believe that an acceptable mechanism can be worked out for keeping your office currently advised of the extent of involvement of PMA member firms in recombinant DNA research without the necessity for such formalized procedures. Our member firms, which are so engaged, could assure your office of the existence of institutional biohazards committees, a concept which the industry has already endorsed. Minutes of the meetings of such committees could be made available in an edited form which would provide the safeguards which are considered necessary to protect intellectual property rights and at the same time provide the necessary assurances of compliance with the safety provisions of the Guidelines regarding physical and biological containment levels. Such minutes could be made available to appropriate officials of your office, provided that the information thus provided would be protected from public disclosure.

It is suggested that the details concerning allowable exemptions from the requirements, as published, can best be discussed at a meeting between representatives of your office, the PMA and affected member firms as suggested earlier by Dr. John G. Adams of our staff. I am confident that such a meeting will satisfactorily resolve the administrative problems involved and achieve your purpose in assuring compliance with the Guidelines by the pharmaceutical industry. We are pleased to offer our cooperation in your efforts to provide guidance in this new and important field of research and will look forward to hearing from you in the near future concerning the above suggestion.

Sincerely yours,

C. Joseph Stetler

Enclosures

For example, the major questions being studied by the Lilly research staff, and the thousands of related questions, change regularly as new information leads to the refinement of some questions and the abandonment of others. Here are just a few of the major long-range questions we are currently trying to answer:

* Can we induce your body to create its own anti-infective agents by influencing the amount and type of antibody molecules secreted by cells that reside in your bone marrow?

* What factor will trigger your body to synthesize a substance that makes it difficult for fatty deposits to adhere to the interior wall of your arteries?

* Can we identify the mechanism that controls the reproduction of normal body cells and fails to do so in malignant cells?

* What chemical will act selectively on the enzymes in a soybean plant to improve the efficiency with which the plant uses sunlight to produce the carbohydrates essential to growth?

* Can we induce microorganisms that produce their own nitrogen compounds for self-made fertilizer in the roots of some plants to do the same sort of work in the roots of other plants?

* Can we change the characteristics of certain organisms to permit them to thrive in the intestinal flora of cattle and hogs, thus reducing substantially the livestock's need for expensive feed?

Finding the answers to these and another thirty or forty questions similar in scope, diversity, and complexity constitutes the major efforts of the Lilly Research Laboratories. It is a massive effort, involving more than 2,600 people--that's almost nine times as many people as are in this room today--and requiring well over $100 million a year.

Obviously, such an undertaking must be guided by some basic principles and strategies. Let me briefly mention what we think are the important guidelines in our research program.

The starting point is superior people. They must combine intelligence with technical training, initiative with perseverance, ingenuity with caution, personal enthusiasm with scientific conservatism, and intellectual freedom with organizational needs. Underlying all of this, of course, we encourage a fierce and personal sense of scientific integrity.

With such people, we do not hesitate to embrace the strategy of attacking the truly challenging problems. The emphasis of Lilly research is directed toward the solution of significant and pervasive problems in human health and agriculture. In such a strategy, we know that three basic conditions prevail:

pounds and, on occasion, capitalize on pure chance. One compound originally thought to have use against tumors in humans disappointed us in this regard. Further screening of its activity, however, revealed its ability to combat enteritis in swine, a use for which it is now being extensively tested.

New research techniques, of course, are vital to new research accomplishments. One new technique, called recombinant DNA, or genetic splicing, has stirred considerable controversy about the risks compared to the benefits—not unlike the controversy that has centered around the experiments of scientific groundbreakers from Louis Pasteur to Jonas Salk.

Genetic materials—chromosomes and genes—are composed of DNA, which almost all living things use to store their hereditary information and direct all their normal life processes. Man now has the actual ability to recombine this genetic material in some bacteria and the theoretical ability to recombine hereditary characteristics of plants and animals. This presents the great hope of altering organisms to the enormous benefit of mankind. Certain risks are attendant to the process, but we believe them to be quite low. We believe the risks are assessable as the technique evolves and that they are manageable by competent, conservative, scientific techniques. We support in principle the guidelines established by the National Institutes of Health and follow them meticulously. It would be unfortunate, indeed, to have restrictive legislation on this research, as it would on other research.

Basically, of course, what science is looking for is knowledge, and man's progress for twenty centuries or more has been built on the acquisition and proper use of new knowledge. To eliminate a field of research because of the possible (and widely exaggerated) dangers of knowledge would contradict the very purpose and value of scientific research.

Perhaps now you have a better understanding of all the talent, time, effort, money, and technological systems that fuel the Lilly research effort. As shareholders, you may also be wondering about the practical results of such a massive program. Before making any comments about results, let me remind you again of the unpredictability of science and the long odds against test compounds' becoming marketed products. At this point in time, we have more than thirty new compounds being evaluated by carefully controlled use in human medicine and agriculture. The new drugs for human medicine are undergoing clinical trial usage in patients. Some of them are being evaluated for their effectiveness in the treatment of major disease problems, such as heart disease and arthritis. Others are being tested for use in significant, but not widely occurring, medical conditions, such as psoriasis. As they have been for decades, new antibiotics are an important part of our clinical testing program.

In the field of agriculture, the new agents for use in crops and animals are being evaluated in realistic conditions outside the laboratory. For crops, these tests range from the rice paddies of

RECOMBINANT DNA RESEARCH:

A New Frontier in Biological Science

An interview with

Irving S. Johnson, Ph.D.

Vice-President, Lilly Research Laboratorie
Eli Lilly and Company

April, 1977

Introduction

A new frontier has opened in biological science. Through a series of spectacular developments that date from the breaking of the genetic code in 1953, man now has the theoretical ability to recombine the genetic material from different species of plants and animals. This presents the great hope of altering these organisms in ways that are highly beneficial to mankind. Yet it also raises the question of risk, of the potential for negative effects from scientific procedures that have such far-flung application.

The possible risk from such research seems to vary greatly with the type of experiment. Thus, in 1974, leading American biologists called a moratorium on certain genetic recombinations until safety guidelines could be developed. The two-year moratorium ended last June, when the National Institutes of Health issued their recommendations on the subject.

Concern and, inevitably, some misunderstanding continue, however. Thus, Congress is now holding legislative hearings on genetic recombinations, and, in recent months, the news media have often discussed the benefits and possible risks from such research. To provide shareholders with background information on the general subject and also to explain Eli Lilly and Company's own work in this area, the company presents the following interview with Irving S. Johnson, Ph.D., vice-president of Lilly Research Laboretories.

How is foreign DNA inserted into a bacterium?

Scientists have recently discovered a whole new class of enzymes that can cut and splice the long DNA molecules in specific ways. The compounds work with genetic material from any source. They are used to attach foreign DNA fragments to the DNA of either bacterial viruses or plasmids. The latter are bits of DNA that exist apart from the chromosomes in certain bacteria. Under the right conditions, plasmids and viruses have the capacity to enter the bacterial cell and then reproduce themselves once inside. When linked appropriately to a piece of foreign DNA, they will carry it into the cell and reproduce it along with their own genetic material.

What do you gain from this?

Suppose, for example, that the foreign DNA fragment was the gene that codes for a specific hormone, such as insulin. You might eventually develop a new strain of bacteria that could synthesize it directly. This could be much more efficient than the current system of extracting the hormone from the glands of animals. At the very least, it would supplement the supply available from animal sources.

There's a whole range of other possibilities, of course. Certain soil bacteria, for example, can convert atmospheric nitrogen into nitrogenous compounds that plants can use as food. If the gene group responsible for this process could be incorporated into wheat or other crops, they might eventually be able to pull their own nitrogen fertilizer out of the air.

The practical benefits sound fantastic. Does the technique have any applications in basic research?

Yes, and they're tremendously important. Recombination techniques, for example, can be used to map the chromosomes of an organism. This means to locate the specific gene or genes responsible for various functions, such as photosynthesis or control of cell replication. When the gene of interest has been located, the same techniques can then be used to produce it in quantity for additional studies. The mapping of chromosomes will lead, almost inevitably, to new biochemical information about disease processes of all kinds.

DNA recombinations can also help us learn how cells turn their genes on and off in producing the endless array of compounds needed by the organism as a whole. Knowledge of this kind, for example, will probably be necessary before we can actually transform bacteria into little production units for antibiotics or hormones. The important point here, however, is the synergism that comes with new basic information. A clarification of gene-control mechanisms, when combined with existing knowledge, could easily generate a totally new lead or insight in another area.

Great! But how about safety? Do the NIH guidelines really give adequate protection?

The majority of biologists feel that the guidelines, though conservative, are reasonable given the

The safety procedures sound elaborate. But what are Lilly's current research interests with recombinant DNA?

We're attempting, among other things, to use the new techniques with antibiotic-producing microorganisms. Our objective is to create modified organisms that can either synthesize new and better antibiotics or produce an existing one more efficiently. This kind of work isn't entirely new. Lilly and many other laboratories have been modifying organisms with chemical and physical agents for years.

Lilly also hopes to use DNA recombinations to produce hormones and other medically useful proteins. Some of the compounds we have in mind are simply not available in any significant quantity at the present time. With others, our main objective will be to produce them more efficiently.

In closing, Dr. Johnson, could you mention a few of the long-range possibilities from research with recombinant DNA?

O.K. But remember, the time frame on such things is impossible to predict. And many developments may never occur even though, from our present viewpoint, they seem almost inevitable. Scientific revolutions somehow never seem to produce all that's expected of them in their infancy.

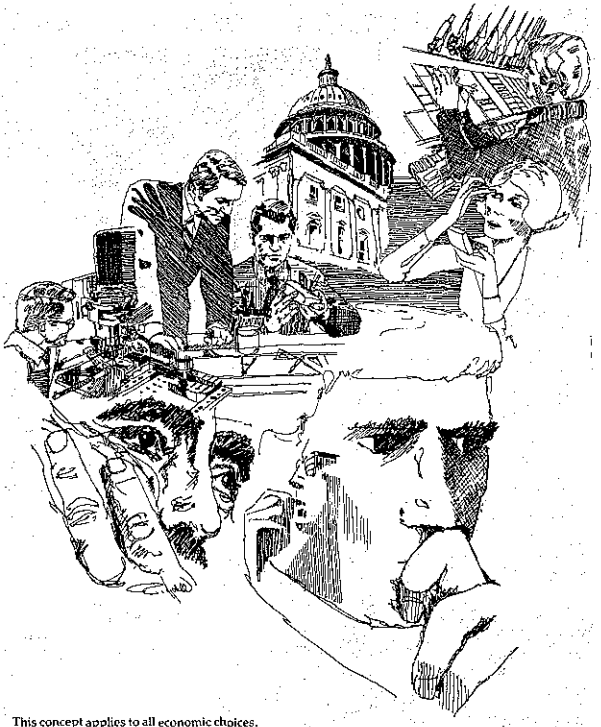
Probably the most significant thing about DNA recombination is the enormous increase in basic knowledge it can provide. Eventually, for example, it could lead to a complete understanding, in strictly chemical terms, of pathologies such as cancer, heart disease, malfunctions of the immune system, and even the aging process itself. Knowledge of this kind, obviously, is our best hope for real progress in all these areas.

How about some of the more tangible benefits?

The theoretical possibilities—and, remember, that's all they are at present—sound like pure science fiction. Some of the things most frequently mentioned are: tailor-made microorganisms for energy production and pollution control; plants that are resistant to diseases, pests, and drought; a whole range of hybrid plants, such as a "pomato" with tomatoes above ground and potatoes on its roots; beef cattle, swine, and poultry designed for taste and efficient production; completely new species of plants and animals; and, finally, cures for genetic diseases through replacement of the defective DNA.

None of these things is just around the corner. Some may not even be possible. Society as a whole may eventually find others undesirable. Nonetheless, it is time—in my opinion—to begin a cautious exploration of this revolutionary research technology that science has provided. The potential benefits are enormous and the risks, though somewhat indeterminate, can be assessed and managed by responsible scientists.

Decisions on economy will affect our future



This is the last in a series of articles dealing with the basic concepts of the American economic system. The series was prepared following a nationwide survey involving people from all walks of life. The study revealed that Americans have a basic faith in their economic system. It also indicated that many people have difficulty describing how the system works and how they are involved in it. This last article discusses the choices that will have to be made in the use of our economic resources.

In this brief description of our American economic system, we have tried to answer basic questions: What are the special roles of consumers, producers, resources, and governments? What principles affect how it works? What are the dimensions of our economy?

The need for choices

In answering questions like these, it becomes obvious that our economic system is not a perfect one. All of our needs and desires cannot be fully satisfied — nor will they ever be in a world of limited resources.

Throughout history, many societies have attempted to solve this problem by dictating what individual needs and wants should be — and by controlling how these needs and wants are met. Yet economic freedoms and personal freedoms have a way of interlocking. When individuals are told how they must conduct their economic lives, and where there are obstacles to such economic freedoms as spending choices and career choices, personal freedoms are inherently involved.

In the American economic system, decision-making is shared by consumers, producers, and governments. Our challenge — and privilege — is to make wise choices in our use of economic resources, to best satisfy our private and public needs and wants, now and in the future.

Considering alternative benefits

What benefits do we gain when we make a particular economic decision — compared with the benefits we might have gained by making another? We must always consider the alternatives.

What we are discussing is an economic concept known as *opportunity cost*. When limited resources are used, some benefits are gained, but some are also sacrificed. So there is a "cost" involved in our choice.

This concept applies to all economic choices. For instance, in our own lives we make choices like these:

Spending for things today, or saving for the future.

Balancing spending for food, clothing, and shelter against spending for entertainment and recreation.

Undertaking extra work, or spending that time on leisure.

Comparing the potential benefits of higher education with the cost and sacrifices it normally requires.

There are also key public issues that require choices:

How much government involvement in our economy is necessary for its continued well-being? In what areas should there be less involvement? In what areas, more?

How can we balance national growth with conservation of natural resources and protection of our environment?

How can we evaluate the long-term economic and social costs and benefits of various government programs?

How can we hold down inflation and yet stimulate the economy and expand employment?

How can we preserve the benefits of competition in our American economic system and still meet the needs of the less fortunate?

Answers to such questions as these are anything but simple. Yet these issues directly affect our own future, our children's future, and our nation's. Under our American economic and political system, such answers depend upon the choices we all make.

For 200 years, America has prospered, defended individual freedoms, offered hope and opportunity to people from many lands and of many beliefs, and met challenges with confidence and determination.

Our economic system has been a major element in this tradition. This system must continue to be a vital source of strength and achievement if we are to maintain our progress in the years to come.

* * *

It is hoped that this series of articles has given you a better understanding of the American economic system and how you play an important part in it. This series will be worthwhile if it has increased your desire to learn more about our economic system and to use that knowledge to make better economic choices for yourself, your family, and your nation as it enters its third century.

These articles, serialized from a booklet — *The American Economy . . . and your part in it* — are reprinted with permission of the publishers. Prepared by The Advertising Council, Inc., and the U.S. Department of Commerce in cooperation with the U.S. Department of Labor, the booklet is still available in an extremely limited quantity to Lilly employees free of charge from the Employee Communications Department, MC339, Eli Lilly and Company, P.O. Box 618, Indianapolis, IN 46206.

Special thanks to Ron Hydell (MC-audio-visual services), whose line drawings illustrated this series.

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Former officers Beck and Koffenberger die

Burton E. Beck

Burton E. Beck, a member of the Board of Directors and former Lilly president, died Sunday, March 27, in Hawaii.

Mr. Beck, 59, was president from April 1969, until his retirement in January 1972. He was elected to the presidency following four years as executive vice-president. Since his retirement he had been a rancher at Sonoita, Ariz.



Richard D. Wood, Lilly Board chairman, said: "Burton Beck was a man of great talent and energy. He combined strong motivation and hard work with an unusual skill in working with people to manage change in a growing worldwide business."

Beck was born in Indianapolis Jan. 31, 1918, and attended the former Park School, where he participated in football, basketball, and track. He received a Bachelor of Arts degree in psychology from Cornell University in 1939 and joined Eli Lilly and Company as a trainee that same year. He later worked as a time-study observer before entering the United States Army in January 1942.

A battery commander in the field artillery with the 80th Infantry Division, Beck saw action in France, Austria, and Germany. His decorations included the Purple Heart and the Bronze Star. He was discharged as a major in early 1946 and returned to the company in April. Later that year he became the first commander of the Eli Lilly and Company American Legion Post.

Beck's first assignments after the war were chief of placement and wage studies and, later, chief of incentives and job evaluation. He was promoted to assistant manager of methods and standards in 1948 and became a staff assistant to the vice-president of production in 1951. The following year he was named executive director of personnel and public relations.

Mr. Beck became vice-president of industrial relations in 1958. A year later he was elected a member of the Board of Directors and became president of Eli Lilly International Corporation. He played an active role in directing Lilly International's affairs by personally visiting most of the affiliate companies abroad, 25 of them at that time.

Following his experience with the international business of the company, he was named group vice-president of marketing and domestic subsidiary operations in 1964.

At the time of his retirement, Mr. Beck was a member of the executive committee of the Board and was chairman of the management board for Elanco Products Company. He also was a member of the board of directors of Lilly International and was chairman of the board of directors of Elizabeth Arden, Inc.

During the time that Mr. Beck headed the company's personnel activities, the Board of Directors approved the Lilly Employee Savings Plan, an improved retirement plan, additional holidays, and a liberalized vacation program.

From his diverse experience, Mr. Beck developed a broad view of the functions and responsibilities of a large corporation. He believed: "A business is not just a creature of production and profit. It provides important social and work satisfactions for its employees. It's a continuing source of new products, new technologies, and improved living standards. Today, more than ever before, business serves the needs of society as a whole."

Mr. Beck assumed numerous civic, business, and educational responsibilities in addition to his career with Eli Lilly and Company. He was a member of the Park-Tudor Foundation and was chairman of the finance committee of the Lilly Endowment, Inc., board of directors. He was president of the Fair and Rodeo Association of Sonoita, Ariz.

Mr. Beck met his wife, the former Bettie Ann Putnam, of Cleveland, while both were students at Cornell. They have two daughters, Elizabeth Ann, of Indianapolis, and Mrs. Timothy T. Tomlinson, of Seattle, Wash. A third daughter, Sarah Jane, died in 1966.

Mr. Beck's father, Earl Beck, also a long-service Lilly employee, was executive vice-president at the time of his death in 1954.

James E. Koffenberger

James E. Koffenberger, retired vice-president and former member of the Board of Directors, died March 10 in Sarasota, Fla. Mr. Koffenberger, 60, retired in 1974 after completing a 35-year Lilly career.



Born in Cincinnati, Mr. Koffenberger was graduated from high school there in 1934 and received a Bachelor of Science degree in pharmacy from the Cincinnati College of Pharmacy in 1938.

He joined the company in 1939 as a sales representative in Covington, Ky. Following duty in World War II, Mr. Koffenberger served in a hospital specialty territory in Cincinnati and in the product promotion and sales training department before being named manager of the Memphis district in 1953.

He returned to corporate headquarters and held positions in sales, industrial relations, and merchandising. He was elected vice-president of market development in 1965 and to the Board the following year.

Subsequent positions he held were vice-president of sales, vice-president of marketing development and planning, and vice-president of corporate affairs, his position at the time of his retirement.

Mr. Koffenberger was a member of Kappa Psi, professional pharmacy fraternity, and Phi Chi, pharmacy honor society.

Survivors include his widow, Dorothy; a daughter, Mrs. Ross Herrick, Jr.; and a son, James E., Jr., a Dista sales representative in Illinois.

Annual Report for 1975 receives international honors

The company's 1975 Annual Report, "The First One Hundred Years," has been displayed in two of the most prestigious graphic shows in the country: the Chicago '76 exhibition at the Chicago Civic Center and *Art Direction* magazine's Creativity 76 exhibition at the Conrad Hilton in Chicago and at the New York Hilton. The report was designed by Design Associates of Indianapolis, which entered the annual report in the competitions.

Out of thousands of entries judged for the Chicago '76 show, only 200 are chosen for display. Acceptance into the show is the award, and each accepted piece is considered a winner.

Entries in the Creativity 76 show include catalogs, logos, book designs, promotional pieces, annual reports, and television commercials. The competition is international in scope, open to all visual professionals, and seen by thousands of people. The 1975 Annual Report was one of 400 winners, all of which are published in *Art Direction's Annual*, which is considered an indicator of excellence in advertising.

In both competitions the judges look for concept, copy, art, photography, and production as well as graphic design.

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Dr. JOHNSON. I think that is a difficult and complex question. I will try to answer it as explicitly as I can. I think the intent of the regulation of the bills pending before the Congress and the intent of the guidelines is not really to restrict research, except for the forbidden areas. Our problem, in terms of disclosure of what we hope to do in great detail is the matter of patents on proprietary information. We have no problem on disclosure and registration on a confidential basis. We do this now in many of our endeavors, but particularly with the FDA in terms of an investigational new drug filing. This information, however, in a highly competitive industry, if published in the Federal Register, for example, does give information to our competitors and this is a highly competitive industry and that is what we are primarily trying to avoid. We do not have any nefarious schemes to do anything that is evil. We would like to be able to protect an investment. And this is a very significant investment.

Mr. THORNTON. Of course, isn't that what a patent is supposed to do, to protect you while requiring a disclosure?

Dr. JOHNSON. That is correct.

And in terms of production, in my talk at the National Academy of Science open forum. I outlined some testing procedures which I would advocate for any organism which might go into production. We are perfectly able to assess, in our laboratories, the pathogenicity of an organism, its sensitivity to antibiotics—and we can easily assess in the laboratory its ability to colonize the intestinal tract. We do many of those things routinely. We do it with great containment and we can do it with immuno-deficient animals, with germ-free animals and we have a high capability to investigate any potential risk. We can do so and if such a risk existed, we would have to ask very serious questions about risk versus benefit and we would ask people to participate with us in this discussion.

One other observation I might make about industrial work in this area, while we are still discussing the legislation and guidelines, is that in the United Kingdom, as I am sure you are aware, their regulatory apparatus is already in place and operating. There they operate under the Official Secrecy Act and industrial protocols are submitted for approval in terms of safety. Patents have been applied for already by United Kingdom companies. I am not advocating that approach necessarily. I am just indicating that it is already in place and operating and that the United Kingdom has significant industrial capacity in this area. I also understand that many of the Western European countries intending to go to that type of organization, the so-called GeMag organization. I have suggested that one of the primary areas of industrial application of this technology is in the fermentation area. Countries like Japan have a highly developed fermentation industry and have no guidelines at all. I would have to assume that they are proceeding in this area with great dispatch.

Mr. THORNTON. I believe that the institutionalizati n of the standards in England has resulted in some rather strict penalties being attached to violations of the standards, as well.

Dr. JOHNSON. I spoke recently, within the last month, in fact, to a member of the United Kingdom GMAG Commission. He did not indicate any such thing to me, I do not know whether by omission or not.

Mr. THORNTON. It was related to us in earlier hearings that there were some sanctions in the form of fines and other penalties.

try, have made to anticipate and evaluate the hazards of the research and take the proper protective steps as reflected in the Asilomar Conference and the NIH guidelines. But I have not been yet able to fully satisfy myself that there is ongoing an extension of that process. What we are sometimes describing are impact analyses and technology assessments that look into the future as to what will happen if we are completely successful in what we do. And we do it very safely. And we create whole new industries. We release whole new strains of new bacteria, and we get to the point where we can affect the genetic traits of human beings or higher mammals. Has there been that kind of analysis—or maybe it is too much to dignify with the term "analysis,"—"speculation" might be better—in an effort to anticipate what will happen 150 years down the road?

Dr. JOHNSON. I think your comments about assessment are very pertinent in this admittedly very controversial area and an area that has been highly polarized or politicized.

I do not think there has been any careful assessment by everyone. I regret that, because I think one can make a careful assessment And I think you can come out with a rather good feeling about it. Let me give you a couple of examples.

There has been considerable concern when we first sent men to the Moon that we would bring back horrible pestilences. My personal assessment of that was that it was very unlikely. I considered the fact that the Moon was operating essentially in a vacuum, that it was extremely cold, there was no evidence of water and by assessment as to whether life might be there, at least as we know it, was that it was very unlikely. In spite of that, Mr. Brown, the Government spent something like $40 million in trying to provide for that eventuality. And I have to say I was amused as I saw the capsule come plunging into the ocean, a rubber ring was put around it, a frogman swam over, opened the door, inhaled deeply, and said, "How are you? Are you OK? That is not aseptic technique. In fact if these gentlemen brought something back, it was already in the ocean and in the lungs of the frogman. As they got aboard the ships, their hands were clasped and arms were thrown around their shoulders and so on and so forth.

I think you can make similar sorts of assessments in this area.

Mr. THORNTON. And then they put them into isolation.

Dr. JOHNSON. You are absolutely correct.

But *E. coli*, for example, which has been used for years in hundreds and hundreds of laboratories, has not caused epidemics of diarrhea and other things. It has been used as a tool for genetic research.

I have indicated that I think that the mechanism of antibiotic resistance, if you make a careful assessment of it, makes it highly unlikely that the insertion of a piece of foreign DNA would necessarily give the ability to degrade antibiotics to *E. coli*. It still has to make a cell wall. I think you can make careful assessment of the probability that this will occur.

In my talk to the National Academy of Sciences forum I indicated a rather rigid series of tests that one might put such an organism through prior to its being submitted for any type of production.

Mr. BROWN. You are responding rationally. And it would be better for people in this field to do so. The reaction of Congressmen which are frequently neither rational or better informed——

genes from nitrogen fixing bacteria can be put into plants and whether they will be able to function if that is done is unknown. These things have not happened yet and I think that a great many of these things in all probability will not happen. When some new technology develops its utility, usually lies somewhere between two extremes. It is not as bad as the pessimists think and not quite as good as the optimists think. Its utility, is usually somewhere in between and I think it will be true of recombinant DNA technology also.

Mr. BROWN. You might just give us on behalf of your industry your reflection as to what would be applicable 75 years——

Dr. JOHNSON. Let me say one other thing about the agricultural area. To my knowledge the only research in this area is in the Department of Agriculture. I am not aware of any industry involvement in this area at all.

Mr. BROWN. The National Science Foundation is supporting research in this area, very likely.

Dr. JOHNSON. I expect so.

Mr. BROWN. I just want to conclude by commenting that there are many people, some in Congress, who feel that we do need to make these kinds of future, analysis-type of projections, and we have made them in connection with some of our current developments. When we initiated them a generation ago, we might have structured the development a little bit differently.

Thank you.

Mr. THORNTON. Thank you, Mr. Brown, for a very excellent line of inquiry.

I think it might be useful, pursuing that just a step further, to consider for a moment the difference between two possible utilizations of this technique—and I believe Mr. Brown first brought this to the attention of our subcommittee. One of these is where the recombined, genetically altered microorganism is released and performs a function, such as nitrogen fixation. The alternative is the one which you accented in your testimony, I believe, where fermentation or the growing of yeast, or some such process, is used and the product of the process, for example, insulin or an antibiotic, is separated from the organism and the organism itself is never, at least hopefully, intentionally released.

Dr. JOHNSON. It is destroyed in the process.

Mr. THORNTON. It is destroyed in the process. Do you think that there is a significance between those two uses? And is that distinction recognized in the guidelines?

Dr. JOHNSON. My personal view—and I am speaking primarily as a scientist in this regard—is that there is a distinction and I think that the guidelines do not really speak to the matter of plant research and agricultural research, in any great detail largely because there is no experience as yet in that area. All of the experience has been essentially in putting a few genes from fruit flies or a few other organisms into *E. coli*. The technology, while it exists in theory, to do the things you are asking about, Mr. Brown, no one has yet attempted to do. I assume people are thinking about it. There are great technical difficulties associated with that and the techniques which have been used so far and the amount of work that has gone on may well not be applicable to the plant and agricultural area. Different technology

Dr. JOHNSON. That is correct. There are several techniques that achieve something like this which are not included in the guidelines and my personal feeling is that they probably should not be either. One is cell fusion, where one just chemically has the ability to make two cells fuse and form a common genetic pool. What happens in the laboratory in this case is that much of that information is lost because it does not have any evolutionary advantage to the fused organism. That organism normally does not divide and does not multiply. I have mentioned chemical change by ultraviolet or X–rays or things of this sort. It is not covered in the guidelines, nor do I think it should be. We have had many years of experience with it and again, you alter native DNA by this technique and that is not a far cry in my mind from inserting a piece of different DNA. The native DNA that you have chemically altered is different, it is not natural.

In terms of natural combinations of DNA, I might also observe that many of these do not really function well, for example, when you try to cross species, you can cross lions and tigers though they usually are not fertile. But when you try and cross species very broadly, you do not get viability and you do not get multiplication. And I think that is a good guideline which has been set up by some higher authority which seems to function rather well.

Mr. THORNTON. In that regard, I think this might also help me to understand what is involved here. I had the idea, as I started these hearings, that you were indeed making transpositions of a great chunk of genetic material in one organism into another organism and ending up with a higher organism of some kind which might look like neither or both. The impression I am now getting is that the level of achievement or research currently is that the parent, the main unit which may be *E. coli*, remains an *E. coli*, that it does not change and become something else, but it has some additional genetic information added to it.

Dr. JOHNSON. That is right. Which may or may not function in some way.

Mr. THORNTON. Which may or may not function.

Mr. BROWN. It may be a blue-eyed instead of a brown-eyed *E. coli*.

Dr. JOHNSON. I think, if you inserted the gene for bovine insulin, for example, the *E. coli*, that you would not be able to extract milk from it.

Mr. THORNTON. The next thing then I was a little startled yesterday to learn that a gene, the information that we refer to as a gene, may contain a number of bits of information drawn from totally different parts—

Dr. JOHNSON. This is the overlapping information.

Mr. THORNTON. Overlapping or discontinuous information which may be present to cause a particular function to occur.

Dr. JOHNSON. This is very new information and would probably not have been recognized if research in recombinant DNA had not been going forward. And there is bound to be new information and new thoughts as this work progresses. I think that it is compelling that there continue to be flexibility on guidelines and regulations based on the information as it comes forward, which may lead us to be more strict, which I doubt, or may well suggest that we have even over-

SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

TUESDAY, MAY 3, 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 9:10 a.m., in room 2318, Rayburn House Office Building, Hon. Ray Thornton (chairman of the subcommittee) presiding.

Mr. THORNTON. This hearing will come to order.

This morning the subcommittee is continuing its hearings on the science policy implications of the DNA recombinant molecule research issue.

Our subject this morning is going to be examination of local actions concerning this research, especially the action taken by citizens of Cambridge, Mass., Princeton, N.J., and Ann Arbor, Mich.

We're going to consider both the potential correlation of these actions with other State and Federal approaches to the regulation of research as well as the question of public participation in scientific and technical decisionmaking. DNA recombinant research will be the focus of our attention, but we're going to keep in mind that this particular case study is central to the broader consideration of these overriding issues.

We are going to ask our witnesses this morning to work as a panel in order to assist our subcommittee in our consideration. Mr. Albert Wheeler has yet to arrive, but we have Dr. Sheldon Krimsky, who is with us, Mrs. Hessy Taft, and Dr. Jonathan King.

Dr. Krimsky is the associate director of the program in urban, social, and environmental policy at Tufts University. We are very pleased to have you in attendance at our hearings this morning, Dr. Krimsky, and at this time I would like to ask you to begin.

[Biographical sketch of Dr. Krimsky follows:]

DR. SHELDON KRIMSKY

Dr. Krimsky received his baccalaureate degree from Brooklyn College and his master of science from Purdue University in physics. He continued his studies in classical and modern philosophy, specializing in the philosophy of science, at Boston University where he was awarded his doctoral degree.

Dr. Krimsky has taught philosophy as assistant professor at the University of South Florida and as lecturer at Boston University.

After a year of post-doctoral studies in economics and environmental policy, Dr. Krimsky joined the faculty of Tufts University's Graduate Program in Urban Social and Environmental Policy. Presently, he is associate director of the program and lecturer in political science.

leave if the research were prohibited, members of the review board commented that redistributing the academic wealth might prove beneficial to our society.

There was considerable skepticism in having a "lay" citizen board tackle a debate that divided many scientists. The Cambridge experience showed that the process was possible, but not that it was generalizable. Conditions for replicating that process are complex. Replication entails a choice of self-confident, unyielding citizens, who are prepared to devote substantial amounts of time; a carefully worked out plan for educating the citizenry and some instrument for handling the analysis of information.

While the review process was probably a milestone in public participation for an issue of such a technical nature, let's not forget that 8 citizens were willing to spend an average of 8-to-10 hours per week for 4½ months. I estimate it took 1,300 person-hours before a recommendation was finally made. It's not every issue that will generate this degree of dedication.

The Cambridge board likened itself to a citizen jury whose responsibility it was to examine the controversy within the scientific community. The board met twice weekly for 3-hour sessions. It established a schedule whereby adversaries testified on alternate weeks. It drew in testimony from outside the local community through open-line telephone conversations. It called upon scientists to explain technical concepts, present simplified models of biochemical events and draw upon analogies to foster understanding of the technology. In a 5-hour marathon mock courtroom session board members served in a jurylike role, while advocates on both sides of the controversy presented arguments, cross-examined one another and responded to questions raised by the citizen board.

THE OUTCOME

In a unanimous decision—which for the city of Cambridge is a rare and short-lived phenomenon—the citizen review board voted to permit P–3 recombinant DNA research if additional conditions were adhered to beyond the NIH guidelines. The principal concerns of the board, which were reflected in its recommendations, and ultimately put into a city ordinance, are as follows:

Stricter monitoring requirements should be imposed under laboratory conditions. Given the way that technology has turned against us in so many areas, it was quite a modest proposal to require that all the assumptions made about laboratory safety such as the improbability of escape of laboratory organisms, the enfeeblement of E. coli, protections against the use of antibiotic resistance genes and DNA coding for toxic substances, that all these be validated. The board also called for a registry of laboratory workers for long-term epidemiological studies. It also requested that—

No agency should serve as both regulator and promoter of the research.

Additional forums must be set up to examine the broader social and ethical issues raised with the technology.

Monitoring of the research should not be the exclusive responsibility of the principal investigator or the institutional biohazards committee.

that they would surely have their own tacit agenda, I would encourage a pluralistic decisionmaking model that is likely to be more effective in promoting public confidence in the process.

I would like to say a few more remarks apart from my written testimony.

Mr. THORNTON. Please go right ahead, Dr. Krimsky.

Dr. KRIMSKY. We must, it seems to me, as a Nation, begin facing up to the social and ethical consequences of recombinant DNA technology. It is not premature to establish a national dialog to consider what, if any, limits should be placed on the research and what controls should be placed on its industrial and clinical applications. Thus far, these issues have been overshadowed by debates over imminent hazards. Some of the more far-reaching applications are estimated to be within 10 to 50 years off. Some opponents of the research argue that there is a direct causal link between recombinant DNA in the 1970's and baneful forms of genetic engineering in 2050.

I believe we have some options between the alpha and the omega, but we must begin considering who is going to be accountable to the public for how this research is used.

Pharmaceutical companies are very keen to develop this technology, as it may allow them to produce certain hormones cheaply, or scarce blood factors, or odd combinations of plants and insects where species properties are interchanged.

Now all one has to do is to think back to the beginning of the petrochemical industry. We know that almost anything can be marketed. The production sector doesn't simply respond to demand; it creates it. Much of what has been marketed in the name of progress should never have left the research laboratories: PCB's, HCB's, flame retardant carcinogens, DES.

In order to deal with issues of regulation and technology assessment, the Cambridge Experimentation Review Board has recommended the creation of two national commissions. The first would be empowered to establish guidelines, health monitoring standards and licensing procedures for all institutions undertaking the use of recombinant DNA technology. A second commission would consider the social and ethical implications of the use of technology in research as well as its industrial and clinical applications.

We are most fortunate in this most historical episode to have had sufficient warning to address the full range of technical and social issues.

Given that there may be potential costs in not doing the research and potential risks in doing it, our first responsibility is to disclose fully the implications of the technology to the public, define and empirically evaluate the unknown risks, and set up appropriate forums for public participation.

Mr. THORNTON. Dr. Krimsky, I want to thank you for a very thoughtful presentation and for your reflecting on the problems identified in that presentation.

You said that there might be some options available between alpha and omega. I wonder if in this subject matter we're not dealing in options between Scylla and Charybdis, between Scylla of unknown fears, and Charybdis of regulating scientific research, an area in which a great many people are expressing concerns about, really, first amend-

missions, credit and/or placement, as well as the development of general science tests and science evaluation instruments on the elementary and secondary school level both in this country and abroad. I have a master of arts degree in chemistry from Columbia University, and spent 8 years working in biochemical research laboratories prior to my joining ETS. Last year, I was involved in a project for the Federal Energy Administration that required holding hearings on the status of energy education. I am currently a member of the Princeton's Citizens Committee on Biohazardous Research, appointed by the governing bodies of Princeton Borough and Township, whose charge it is to consider the issues of recombinant DNA research in our community.

My experience on the Citizens Committee concerned with recombinant DNA research in Princeton has left me with the unequivocal impression that our society can greatly profit from tapping the wealth of resources that local involvement provides. People who several months ago knew nothing about the issue of recombinant DNA have spent tireless hours of effort and dedicated study to familiarize themselves with the complex issues at hand. Modern technology requires that the gap between scientist and layman be considerably bridged and study committees such as ours supplemented by local public hearings provide, I believe, an effective mechanism for this task.

However, some members of our committee have felt an incredible frustration by the realization that all our efforts are futile without Federal legislation. It does no good to make sensible recommendations in one community if flagrant recklessness were to go on unchecked in a community 30 miles down the road. It is therefore with great enthusiasm that I welcome the present efforts of this subcommittee.

Our Government has long ago made a commitment to support basic scientific research. The outcomes of such efforts have given us scientific world leadership and have become an integral part of our culture. The pursuit of knowledge is an enduring human endeavor, but methods of acquiring knowledge are infinitely varied and the precept of free inquiry cannot be absolute. In principle, no sound intellectual premise can rationalize the concept of forbidden knowledge. In practice, recombinant DNA is a technology where forbidden experiments have already been identified. In groping for viable solutions, the public at large is faced with a profound moral dilemma that tugs, on the one hand, toward encouraging unfettered scientific creativity and, on the other, toward preventing accidents that could have irreversible consequences. The designation of a maximum of 10 national centers designed to carry out experiments on the P_4 level of containment is a wise step in the right direction. Such centers permit the development of what may well be the most promising tool available toward the study of how the genes of living cells are organized and how these genes instruct the cells to carry out their different functions. At the same time, it would minimize the potential hazards that arise from the great number of uncertainties surrounding gene behavior at the present time.

A solution similar to that for the P_4 facilities can and should be equally applicable to research on the P_3 level of containment, at least until we can better ascertain the present ill-defined risks. However, this does not seem compatible with the needs of academic institutions,

10-liter flask—the upper limit usually allowed by the NIH guidelines—contains 1,000 times as many. One wonders at what point the low survival probabilities often quoted become significant.

It is my perception that the NIH guidelines need to be somewhat amended before they are adopted as law. It is not wise to allow any exchanges of a level of biological containment for one of physical containment at the present time since the former is a better safeguard against human error. Nor is there reasonable justification to permit shotgun experiments with any private DNA—certainly not below the P_4 level of containment—until we establish a broader base of knowledge. Furthermore, it would be prudent to install autoclaves in every P_3 facility. These restrictions have been incorporated in the guidelines set forth by Princeton University and in that sense I consider the document an improvement over that of the NIH.

The NIH guidelines are the result of a thorough and extensive study prepared by dedicated scientists who are also concerned with human welfare. Such efforts are highly commendable. But the notion that the people actually involved in the work are the same ones drawing up the rules and enforcing these rules among themselves is contrary to any system of checks and balances which is so fundamental to our way of life. The cosigners of the Berg letter to the National Academy of Sciences may well have shown an unprecedented sense of public consciousness but, as a result of the rapid proliferation of appropriate facilities, large numbers of people are becoming associated with this technique. The implication that scientists can monitor themselves by "peer pressure" only and need no law-enforcing mechanism is both arrogant and naive. Therefore, I have some very serious concerns regarding enforcement of Federal regulation as it appears to be stated in the H.R. 4759 bill. Inspection of a laboratory for mere physical compliance with the regulations is simply not adequate. The requirement for the use of nontransmissible plasmids, for the accurate screening of the purity of DNA before cloning for certain experiments, and for the use of crippled bacterial strains that comply to the biological containment described in the NIH guidelines form the very essence of the powerful means that reduce the potential hazards associated with DNA recombination among more widely differing species.

The NIH guidelines make provisions for site inspection by NIH staff for facilities at the P–4 level of physical containment. Yet there seems to be no provision at the present time for inspection by scientists at the lower levels of containment. The safeguards mentioned above are the easiest restrictions to circumvent—because bacteria are not visible to the naked eye—and are the most likely precautions to want to dispense with—because experiments will be considerably more difficult to carry out with crippled bacteria. Therefore, it seems crucial that Federal inspection be accompanied by specific scientific procedures that test for compliance with biological restrictions both within and outside the laboratory. These matters deserve our meticulous attention regardless of whether they appear cumbersome or slow down certain experiments. If there is any sense of urgency regarding research with recombinant DNA molecules, it must be directed toward a feasible and practical implementation of such enforcement procedures.

The Princeton Citizens Biohazards Committee is considering various aspects of such controls, but we are faced with such overwhelming

"DNA is going to have a tremendous impact on a very wide range of products and processes," he said.

DNA has the potential for significant advances, Mr. Johnston points out . . ., and he noted that:

The prospect of developing products through recombinant DNA techniques has attracted "quite a bit" of interest and enthusiasm among investors.

It is that sort of thing that prompts me to urge Federal legislation to a significant extent.

[The full article referred to follows:]

[From the Princeton Packet, Apr. 27, 1977]

LOCAL SEEKS TO CREATE PRIVATE DNA STUDY FIRM

(By Tom Lederer, Staff Writer)

DNA: the name means deoxyribonucleic acid. For years it meant the fundamental molecule of life, the agent for transferring the language of heredity.

Lately it has symbolized a new and highly controversial form of research in which pieces of DNA from different organisms are spliced together to create new species, unknown in the billions of years of natural evolution.

Now DNA is beginning to mean something else: profits.

While Princeton University awaits final community action on its proposal to build two gene-splicing laboratories on campus, another Princeton organization is attempting to put together the money and experts to create a private research firm to conduct similar DNA research, probably in the Washington area.

The issue of recombinant DNA research is loaded with controversy. The new field has generated equally strong hopes and fears for the future. Paralleling those feelings are equally passionate proponents and enemies of that form of science.

On the one hand the new artificial organisms could lead to incredible advances in the fields of medicine, agriculture and in basic research. On the other hand there is the possibility, however remote, that a new form of disease, perhaps an "Andromeda" strain, could escape from a DNA lab and wreak havoc on the human popnlation.

Johnston Associates, headed by Robert Johnston out of his Pretty Brook Road home, is pursuing that delicate issue in the interest of making significant profits for investors.

Mr. Johnston describes himself as a venture capitalist, a middleman attempting to combine those with risk capital to spend with others with the scientific skills and business savvy to run a private gene-splicing laboratory.

"Our business is raising money for young, high technology companies. We have been mainly in the medical instruments business but now we are moving into the Microbiological field," Mr. Johnston explained this week.

"DNA is going to have a tremendous impact on a very wide range of products and processes," he said.

DNA has the potential for significant advances, Mr. Johnston points out, noting particularly the synthesis of insulin as well as the production of vaccines and hormones that are currently extremely expensive to obtain.

The prospect of developing products through recombinant DNA techniques has attracted "quite a bit" of interest and enthusiasm among investors.

He compares that interest to the excitement generated by the burgening minicomputer business about 12 years ago. Minicomputers are the small computers that began selling for less than $50,000 and weighed less than 50 pounds. They represented the first attempts toward reduction in the size and cost of computers.

In a recent issue of "Science" magazine, Mr. Johnston placed an add seeking an entrepreneur to act as the president of the new company. So far he has had trouble finding someone with talents both in DNA recombinant techniques and in business.

"We've had a fair number of responses. Unfortunately not enough meet our criteria. Most of our respondents have been university people who have little experience in commercial enterprises."

Investing in DNA research is more risky than the normal venture, it appears. A major uncentainty will be the legislation now under consideration by Congress. Mr. Johnston says. He also expects the difficulties in developing the new products to be much greater than predicted.

POSITIONS OPEN

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The University of California, Irvine, Department of Psychiatry and Human Behavior, invites applicants for a full-time position as CHIEF, PSYCHIATRIC SERVICE, Long Beach, V.A. Hospital, with university faculty appointment at professor level. The LBVAH program is a fully integrated component of the UCI medical student and residency training programs in psychiatry. M.D. degree, 3 years of accredited psychiatric residency, California licensure, and evidence of senior levels of academic performance required. *Applications from all qualified candidates are welcome; minorities and women are encouraged to apply.* Send curriculum vitae and names of three references to Dr. E. Mansell Pattison, University of California, Irvine, Calif. 92717.

CHIEF TECHNICIAN-EDUCATIONAL COORDINATOR OF HISTOTECHNOLOGY—Applications are invited from persons with M.S. degree and experience in teaching histotechs, service histology, enzyme and/or immuno-histochemistry. Send résumé, publications, and names of three references to: Dr. L. Vacca, Pathology Department, Medical College of Georgia, Augusta, Georgia 30902.

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ENTREPRENEUR

Wanted, the president for a new company creating products utilizing recombinant DNA techniques; prefer background in this technology and in business. Contact Robert Johnston at 609-924-3131 or Johnston Associates, Pretty Brook Road, Princeton, N.J. 08540.

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To develop a research program to investigate the health and disease effects of environmental pollution with initial emphasis on air pollution. Strong background in biology, physical sciences, and air pollution research desirable. Send résumé and references to: LAWRENCE BERKELEY LABORATORY, Employment Office, One Cyclotron Road, Building 90, Room 3024, Berkeley, Calif. 94720. *An Equal Opportunity and Affirmative Action Employer.*

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The College of Medicine of the University of South Alabama is seeking candidates for three faculty positions in the Department of Microbiology/Immunology. Applicants should have demonstrated ability to teach medical microbiology and conduct basic research in the membrane biology of infectious agents or neoplasia. Research orientation may be in virology, membrane structure or function in pathogenic microorganisms, or in immunological problems associated with membranes. Several levels of faculty membership are open depending on experience. Only applicants who can establish their teaching ability and their research potential will be considered. *This University is an Equal Opportunity Employer.* Interested individuals are invited to apply by direct submission of curriculum vitae and three letters of recommendation to:

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University of South Alabama
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Full-time position in Section of Dermatology, Department of Medicine, State University of New York, Upstate Medical Center. *An Equal Opportunity Employer.* Academic rank commensurate with individual qualifications. Interested candidates should submit credentials including a statement of research interest to: Dr. Fuad S. Farah, Chief, Section of Dermatology, Department of Medicine, Upstate Medical Center, 750 East Adams Street, Syracuse, New York 13210.

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Applications are invited for a faculty appointment in the Department of Medical Microbiology, College of Medicine, effective 1 July 1978. Such appointments are usually made as assistant professor. To teach microbiology, virology, or immunology to medical and graduate students. Research should be at the basic biochemical or genetic level. Postdoctoral experience in microbiology and biochemistry strongly preferred. *Applications from all qualified candidates welcome. Women and minorities encouraged to apply.* Send curriculum vitae and four letters of recommendation to: Dr. Paul Sypherd, Department of Medical Microbiology, University of California, Irvine, College of Medicine, Irvine, Calif. 92717, before 1 August 1977.

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The Laboratory of Genetics, University of Wisconsin-Madison, expects to make two or three appointments in 1977–78 or 1978–79 at the assistant professor level. Applications in plant cell culture, human cytogenetics, clinical genetics, *Drosophila* genetics, and developmental genetics are especially invited, but all areas will be considered. Applicants should send a curriculum vitae, publication list, statement of research and teaching interests, and the names of three references. Send applications to: James F. Crow, Chairman, Genetics Building, University of Wisconsin, Madison, Wis. 53706.

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The Chemical Industry Institute of Toxicology (CIIT) seeks to fill these two important senior positions in its research organization. Both demand a strong research-oriented background, preferably but not necessarily with some experience in toxicology. Both will be heads of departments within the Institute, but participation in teamwork involving other disciplines is essential.

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	Monthly salary and bonus in Saudi riyals	Approximate annual equivalent in U.S. dollars
Professor	6,720 to 7,392	$22,600 to $24,800
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Assistant professor	4,032 to 5,152	$13,500 to $17,300

M.D. degree commands a higher salary. Fringe benefits include free furnished accommodations and annual leave and travel allowance to country of origin.

Send résumé and names, addresses, and phone numbers of three references to:

Mohammed T. Altorki, M.D., MRCP
Dean of the Medical Faculty
King Faisal University
c/o Saudi Arabian Educational Mission
2223 West Loop South, Suite 400
Houston, Texas 77027

Specify teaching experience and date of availability.

2. 1970–1974: On leave from university to serve as director of the Department of Christian Service, Catholic Archdiocese of Detroit, Mich.

Some major civic activities during past 10 years

1. *Current.*—Mayor of city of Ann Arbor, 1975 to present. Member: Steering committee of human resources committee, National League of Cities; housing/community development policy committee, U.S. Conference of Mayors; and executive committee, Southeastern Michigan Council of Governments.

2. *Former.*—First chairman, National Campaign for Human Development, 1970–1973; Member, Michigan Advisory Committee to U.S. Civil Rights Commission, 1967–present; and president, Michigan Conference of NAACP Branches.

STATEMENT OF ALBERT WHEELER, MAYOR, CITY OF ANN ARBOR, MICHIGAN

Mr. WHEELER. Hon. Ray Thornton, chairman, and honorable members of the House Subcommittee on Science, Research and Technology. I am Albert H. Wheeler, mayor of the city of Ann Arbor, Mich. I wish to express my gratitude for the opportunity to appear before you today to discuss various aspects and implications of recombinant DNA research and local government actions. Because of the overwhelming significance of this subject to the future of mankind and because of my awareness of the frequently cited potential benefits and risks inherent in genetic engineering, I approach this with a deep sense of social responsibility and ethical responsibility.

I have given you a written statement, and subsequently I have modified that to some degree. I will not try to read this whole report here because it's just too long.

Mr. THORNTON. If you would like to have your prepared statement made a part of the record, without objection, it will be done.

Mr. WHEELER. Yes. Thank you, Mr. Chairman.

[The prepared statement of Mayor Wheeler follows:]

We refer to Ann Arbor as the Research Center of the Midwest, not solely because of the significant research activities within the University, but also because it is the type of business and industry which we like to attract. Three examples of such existing research facilities that, now or in the future, may have special interests in some aspects of DNA recombinant research are the federal Environmental Protection Agency, the Great Lakes Environment Research Laboratories and the Parke-Davis Pharmaceutical Research Laboratory. Ann Arbor is one of five cities being considered for relocation of the Regional National Institute of Occupational Safety and Health (NIOSH) Center.

The non-white minority population of Ann Arbor is between eight and nine percent, most of whom are Blacks. A significant part, possibly a majority, of this minority population is below the community medians for income and years of education completed. Yet, compared to many other cities in Michigan, it is probably true that a higher percentage of the minority population is either enrolled in post high school education and/or recipients of college and post-graduate degrees.

The Mayor and City Councilmembers are chosen through politically partisan elections, are not full-time and, except for the Mayor, serve without compensation. In recent years, the votes have been divided rather evenly. The present Council is composed of six Republicans and five Democrats. Last month, I defeated my Republican opponent in the City-wide election of the Mayor by one vote.

Another significant local characteristic that should be considered is the question of who, in the community, is performing, planning to perform or likely to be engaged in any DNA recombinant molecule research, or associated activities, and the varied legal relationships between local government and these agencies. Within our corporate City limits, the two most obvious institutions are the University of Michigan (including the University of Michigan Hospital) and Parke-Davis Pharmaceutical Research Laboratory. The Veterans Administration Hospital, with close operational ties with the University of Michigan, is another likely site of such research activities. This facility presents a unique local problem not only because it is a federal agency, but the fact that it is located on a township island within the coporate City limits.

The University of Michigan is an agent of State government that is governed by a Board of Regents which is elected in a statewide referendum. Through the State constitution and State statutes, the University is an almost autonomous agency which is capable of setting its policies and establishing its programs independently of local government. In certain obvious situations, such as streets, water, sewage, fire and police services, it is necessary that the University and City work together. On the other hand, when the necessity for such cooperation is not so clearly obvious, or traditional, as in the case of DNA recombinant molecule research, the University may, and on occasion does, proceed without direct, official communication with the City Council.

B. *The Scientific Public - I see at least three or four scientists to be considered as involved in any issue of the DNA recombinant molecule, nuclear fission, space exploration, laser technology, newly discovered microorganisms which are highly fatal and communicable.*

1. *The expert in the field who not only possesses the knowledge but also engages in the activity.*

2. *The scientist who is an expert in a closely allied discipline but who is not directly involved in the specific research under consideration. Such a person can critically analyze and evaluate not only the methodology, but also the basic skills needed by the research, et cetera in conducting the proposed activity. For example, a microbiologist who understands aseptic techniques and the safe handling of microbes, who is not an expert in DNA recombinant research, could be a valuable asset to the biochemist, geneticist, physician or graduate student who is proposing to engage in this research but who has not had such training or experience.*

3. *The scientist in a field unrelated to the basic research issue but whose expertise should be utilized in the design of the experiment or the facilities. For example, an epidemiologist; or an engineer thoroughly familiar with the roles of air, water and sewage in the transmission of infectious or toxic agents; or an environmentalist who would bring other knowledge.*

4. *The scientist, in a field totally unrelated to the basic issue but who is familiar enough with scientific design and processes that he/she could make critical observations of these matters.*

II. *Local Initiatives:*

A. *What Organizational Process Exists Or Seems To Be Evolving To Deal Deal With Science Issues of Public Policy Importance.*

1. *In the City - no special,formal process has existed in the past and none exists at the moment for the specific purpose of dealing with this type of science issue.*

In the past, the City had an active Board of Health and a modest Health Department staff which worked closely with the County Health Department. However, the responsibilities of both the City and County Health Departments were those common to such agencies in most other communities. If any policy decisions had to be made this was a responsibility of the City Council with advice from the City and/or County Board of Health.

What seems to be emerging: The DNA issue has been a catalyst to me and some other Councilmembers to give serious thought to our responsibilities to the general public and to mechanisms for meeting those responsibilities.

The details of the decision-making process are too lengthy for inclusion in this report. However, if you do not have them already, I believe that the Subcommittee should request this information from the University. I am not certain that any interested party is completely satisfied either with the process or the final official decisions. Nevertheless, a workable compromise was reached, at least for the present, and the process could serve as one model which would be a valuable resource to the Subcommittee as it deliberates on the question of public participation in science policy decision-making.

A few of the many commendable aspects of the University process, from my perspective, are as follows:

a. the initial recommendations regarding the more fundamental issues of Recombinant DNA research at the University were made by an eleven member Committee of University faculty, of whom only four could be classified as biologists, medical scientists or health scientists, as these terms are generally interpreted. The most basic question was whether or not Recombinant DNA research should be permitted within the University. One Committee member cast a firm dissenting vote, the remainder concurred that the research should be permitted but under physical conditions, guidelines and controls which, in many respects, are more stringent than the NIH guidelines.

b. the conduct of an open forum at which highly respected proponents, opponents and critics of the research presented their views and debated issues and where attendees voiced their opinions.

c. the University Board of Regents set aside time for concerned parties from the general public and the University community to present their respective concerns and recommendations.

d. the appointment of a nine member Biological Research Review Committee consisting of several experts in microbiology, virology, epidemiology and Recombinant DNA research; a senior laboratory technician with microbiology laboratory experience; a professor of Chemistry; and, a local pastor with no University affiliation, who was selected from a list of people recommended by the Mayor. A major responsibility of this Committee is to monitor all aspects of Recombinant DNA research activities on campus. It meets regularly and frequently. Copies of its minutes are sent to the Mayor's office and from there to the City Clerk's office for public review.

However, the State should not preempt the prerogatives and initiatives of local government. Therefore, there needs to be a significant dialogue between State and local officials to define their respective roles.

2. Also there needs to be similar dialogue between the ultimate governing bodies of local communities, state and federal agencies and private institutions proposing to conduct the research in a local community.

I, for example, will not abdicate my responsibilities as Mayor of the City to any federal, state or private institution within our political jurisdiction. Just as scientists must re-examine the whole question of the academic freedom and the right of inquiry,so must the various units of government re-examine their respective roles and relationships.

C. Have Local and State Actions Been Successful In Satisfying All Parties That An Acceptable Compromise Has Been Reached

1. It is my understanding that the State government is studying its role in this DNA research issue, but I am unaware of any covert role that it has played, to date.

2. My understanding of the University of Michigan process and ultimate procedure is that most concerned parties are either partially satisfied, temporarily inactive and/or in a wait-and-see posture. It is probably true that those who were completely and vigorously opposed to the research proceeding under any circumstances have not been satisfied.

It is probably equally true that a majority of those who are immersed deeply in the discipline and research with the DNA recombinant molecule may strongly endorse the established regulations regarding the physical environment but fewer may be satisfied with some of the procedures (or the potentials of more stringent lay control in those procedures) dealing with research limitations, monitoring and evaluation.

D. What Effects On National Policies If Evaluations At Local Levels Produce Contrasting Governing Policies

DNA recombinant molecule research is an exciting, revolutionary and infant discipline in which new data and new potentials are being developed at any unanticipated rapid rate. This information is being generated at different localities and under different local regulations, guidelines and relationships between the researchers and local governments.

3. *Comprehensible data which local officials could utilize for self and public education regarding the major issues related to DNA recombinant molecule research,and also concerning various public health and environmental issues related to this research.*

Ultimately, as the public becomes more aware of the potentials inherent to this research, it will be necessary to have candid and believable answers for some of the more sensitive questions of undesirable potentials of genetic engineering.

Albert H. Wheeler, Mayor
City of Ann Arbor, Michigan

political reasons, their very existence or the nature of their existence may rest in the balance.

There are ethical, moral, and legal questions involved and general societal questions, and, therefore, in public participation these voices should be represented.

I think that they have a right to have a voice in a decisionmaking role.

The scientific public, I think there ought to be several types of scientists involved, and one is, obviously, the molecular biologist, who is an expert, and probably a proponent, and worker in the field.

There also ought to be that scientist who is in a related field, for example, microbiology, where there has been training and experience in accepted techniques, the safe handling of animals and materials, and so forth, so that their input is represented in this whole decisionmaking process. For example, chemists, physicists, and other scientists who ultimately may become involved in this discipline may have absolutely no concept of how to handle materials in a safe manner. Somewhere along the line that training has to be done and that voice has to be present.

Then there ought to be a scientist, or scientists, who are epidemiologists, for example, or engineers, because there will be serious questions of both the good and bad effects on the health and welfare of the community. So the epidemiologists ought to be involved.

Then there is the whole question of safety of facilities and the environment, which engineers and environmentalists can certainly deal with.

LOCAL INITIATIVES

In the city of Ann Arbor, there is in the city no special, formal process now nor in the past, to deal with public policy on important science issues such as recombinant DNA.

What seems to be emerging is that some of the city council members and I have been stimulated to look into this question, to determine what our responsibilities are and how we must carry them out. We are exploring a number of ideas such as:

(1) To reactivitate our city board of health, with their charge principally recommending to the city government what steps should be taken, how we should proceed in certain areas on this important question.

(2) The establishment of a policy level committee that is composed of the various units of government within a community. For example, there are State and Federal Government agencies; and then there is the local government. There should be some sort of partnership at the beginning of this process so that then one begins to work in an atmosphere of cooperation rather than in distrust and hostility.

I think that if private industry is involved in recombinant DNA research or production, they too should be a part of this process of policy level communication.

(3) What else is emerging, I propose to put before my council this month of May an ordinance or resolution saying that anyone who intends to engage in any recombinant DNA activities shall provide the city with a notice of intent, specifying the type of research that is planned; the types of facilities to be utilized; that, as a minimum, the

Mr. THORNTON. I had already noticed the word, and was wondering if you were going to raise another area of inquiry.

Mr. WHEELER. No.

I am not aware of any overt actions or activities by the State at this time, except that they are planning, I believe, to determine what they should do.

You asked if the resolutions that were reached in our community were satisfying to all parties, and I suspect that my answer is "No." I think that they are at a peaceful state of coexistence at the present time, and that everybody is a little bit unhappy with what came out. Very often that's what happens with compromises. But at least the compromises created a position were decisions could be made that certain activities could be carried out at specified levels of risk and speed.

What effects on national policies if evaluations at local levels produce contrasting governing policies?

The research is going to be done in different local communities, and it's going to be done under different guidelines and regulations except perhaps for very broad Federal or State umbrella laws.

It seems to me that we cannot avoid differences between things that occur in different local communities. I am not so sure that we want to avoid them, because different experience will occur in one community, or another community, or another community, and if there's a mechanism whereby such varied experiences come to the appropriate official, then they could be used in terms of refinements and revisions of existing policies and regulations.

The question: How can Congress use local information more effectively in evaluating Federal science policies?

The first obvious answer is, I think, we need to have some knowledge of what kind of information you think you want, and what you don't want.

Secondly, we ought to have some mechanisms whereby that information is communicated from local governments to the Congress, and one is, obviously, direct communications. It seems to me that there are existing agencies that could be useful, such as the Mayors Conference, the Governors Conference, and the National League of Cities, Counties or Townships, and so forth. These may be appropriate forums for discussion and the assimilation and compilation of information that can be made compatible with the needs that the Congress defines. This could be then directed to the appropriate agency of the Congress, or designated by the Congress.

The question: What significant local issues are now inadequately addressed at the national level?

I presume this question applies to local, county and State levels, and my concern is: What about institutions or persons who may wish to engage in any sort of recombinant DNA activities, who are not required legally to perform under at least the existing NIH guidelines?

From my getting around and talking with individuals in different areas, there is a suspicion that some of this work is being bootlegged, and I think that the local community has the right to know what is going on. So I think there have to be soon those guidelines that regulate private adventures in this area.

Secondly, I think we need a method or a mechanism, which may have to be worked out at the local level, of dealing with the various

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Birthplace: Brooklyn, N.Y.

Education: B.S., zoology, Yale University, New Haven, Conn., 1962; Ph. D., genetics, Cal Tech, Pasadena, Calif., 1968; post doctoral fellow, Purdue University, Lafayette, Ind.; and postdoctoral fellow, MCR Lab of Molecular Biology, Cambridge, England.

Honors: General Motors National Scholar, 1958–62; B.S., magna cum laude, high honors in zoology; Woodrow Wilson national fellow, 1962–63; NIH predoctoral fellow, 1963–67; and Jane Coffin Childs Fund fellow, 1967–70.

Research and professional experience

Associate Professor, Department of Biology; Massachusetss Institute of Technology, Boston, Mass., 1974 to present.

Assistant Professor, Department of Biology, Massachusetts Institute of Technology, Boston, Mass. 1970–1973.

Jane Coffin Childs Fellow, with Prof. Aaron Klug, MCR Lab of Molecular Biology: Biological Structure Analysis (also worked during this time with U. K. Laemmli and J. V. Maizel), 1969–70.

Jane Coffin Childs Fund Fellow, with Prof. Sewall Champe, Purdue University: Chemistry of Phage and Structural Proteins, 1968–69.

Ph. D. Genetics, with Prof. R. S. Edgar, Cal Tech: Genetics and Morphogenesis of Phage T4, 1968.

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have been essentially excluded from the inner circles of the decision-making on this issue. We have, therefore, been forced to go outside the scientific channels, to our local communities, in the hopes of preventing essentially the covering up of what should be a major public policy decision.

In the controversy over gene transplantation, recombinant DNA, I believe that local action has been instrumental in the protection of public health—it is really in the protection of national health—from a new class of biological hazards. The Cambridge experience also provides a model for the role of public input into science policy, particularly given the absence of a coherent national biomedical research policy. We do not have a focused, well defined national research policy that has priorities that can be criticized or examined for their applicability.

Now, just to back up a little bit, let me review; recognizing the unprecedented biological dangers inherent in reshuffling the genetic heritage of hundreds of millions of years of organic evolution, a small group of genetic researchers moved to set policy in this area. The 150 scientists who met at Asilomar in California were attempting to act responsibly within their limited professional context, and they should be applauded. They took an important step in the necessary direction.

However, the reality was that a rather unrepresentative group set *de facto* national policy, completely sidestepping the normal decision-making processes in a democracy. The Asilomar group:

First. Represented a very narrow sector of the biomedical research community;

Second. Did not include representatives of the public health, occupational health, environmental protection, or other professional sectors.

Third. Had no mandate from any body of elected officials; and

Fourth. Had no accountability to the general public, whose safety it was supposed to protect.

Now, when the National Institute of Health moved into official action, they appointed a set of the Asilomar people as their official Government committee, and simply assimilated the position on genetic engineering developed at Asilomar, which to move ahead with this technology, essentially as rapidly as possible. I think this is a natural position from a group of people who make their living by and are brought up, like myself, doing research, but it's still a position of questionable wisdom.

Prior to the Cambridge City council hearings, the only opportunity for public input—and here under public I include opposition scientists—into policymaking on genetic engineering was a meeting in Washington before the Advisory Committee the Director of the NIH, in which a few hours were set aside for public testimony. The groups active in Cambridge, Science for the People and the Boston Area Recombinant DNA Group and a group in Michigan managed to get together enough money to send down these people to Washington.

By the way, the fact that they didn't pay expenses kept technicians and glassware washers and people at that level from going. That was a week's salary for them to take a day off and fly to Washington.

Not surprisingly, none of our very sharp criticisms were accepted. In fact, the Director's Advisory Committee was just that, an advisory

3. They raised the critical question of accountability and enforcement, without which safety means nothing.

Now I'd like to give an example of something that I believe the City Council understood that the National Insttiute of Health did not understand.

The City Council was able to learn much more about the realities of lab safety because they took testimony from those who actually worked there, and this reveals the nuts and bolts of the problems. For example, the absence of any health monitoring of laboratory workers; the pressure from supervisors to get experiments done as rapidly as possible, in absolute conflict with safety needs of being slow and careful; the absence of worker representation on the local biohazard committees; the absence of any grievance procedure if you feel something is being violated; the intimidation of lab workers who complain openly about safety standards—bear in mind that though supervisors may have job security, technicians do not have job security, graduate students do not have job security. They're often very nervous about speaking openly about violations of procedures; the infestation of laboratories with ants and cockroaches; the absence of a lounge to smoke a cigarette or have coffee in, resulting in the necessity of people smoking and drinking in laboratories, because they get tired, and they can't do a careful, demanding procedure without stopping for a cup of coffee or a cigarette. If you don't have a lounge there, you do it in the lab. Now, the DNA Molceule Advisory Committe doesn't know whether or not my Microbiology Department has a lounge or not. All these, and there are much more thorny procedures.

One very good example, I think, is the setting up of the local Biohazards Committee in Cambridge. Why did they set up a local Biohazards Committee? Because they understood that the accountability of the Institutional Biohazards Committee was to the president or provost of, for example, in my case, MIT, that that committee's real accountability is to make sure that research funds keep flowing into MIT, and where they get in trouble is if something comes up and stops the flow of funds. Now, if there is a problem that has been identified, this is a productive mechanism. If there's a safety problem that's been publicly identified, that committee has to move to correct that problem because otherwise research funds will stop flowing, and so they're progressive.

On the other hand, there is a tendancy to overlook or not to dig too deeply in looking for things that haven't yet come to light because, one, this will result in the holding up of funds, and, bad publicity.

If you really want to protect people from harmful organisms, surveillance and enforcement must be with those who will be the victims, and not with those whose interests are in carrying out research.

In the local Cambridge community they understood this. You have to have safety in the hands of people who are worried. You cannot make a safety committee a group of people who say, "Oh, there's nothing to worry about." It's just a blatant contradiction.

The letter of invitation speaks about compromise. I don't think there is such a thing as a compromise on safety. That's like having a compromise on a nuclear explosion. Either the bomb goes, or it doesn't, and there are no half-explosions. In order to prevent that there be an explosion you have to take extraordinary precautions, just because

set up a cancer registry for the citizens of Cambridge; we have never conducted an infectious disease survey of the community; we have never examined the classes of degeneracy diseases present in the population to see if any of them were due to identifiable pollutants in the community, some of which might be spewing out of industrial or even out of university effluent into the community.

Not that we could solve these problems directly. But the NIH has published a cancer atlas, which gives the incidence of each kind of cancer in each county in the United States. Who is to say that in Middlesex County, in Cambridge, if the local biomedical scientists were to put a little attention there that we could not identify what it is in Middlesex County that's giving people liver cancer?

Because of this, we scientists were out of place when we laughed at our mayor, Mayor Velluci, for asking the chairman of the Harvard Biohazard Committee whether they dumped chemicals into the sewer system. The mayor and the city council understood quite well that the local citizenry was far more likely to suffer the side effects of biomedical research than accumulate any of the benefits. Because they had seen the separation of the scientific community and the lay public, they understood that there was no mechanism to couple the work of research scientists with the real problems of health in the community.

Now, we need to establish a means by which those who suffer from ill health can communicate those realities to those of us who are paid for, in the long run, to improve the national health.

Now remember that national biomedical research policy was formulated in the late 1940's and it represented a substitute for national health insurance and for national health policy, but it was a back door to get money into the health care system.

We have to bring biomedical research back so that it is interconnected with the national health policy. We cannot have research scientists denying that there should be a connection between biomedical research and a health policy, by saying, "Oh, this is only pure research. We're just pushing back the frontiers of knowledge." Fine. But not with the taxpayers' money. Do that on the side, or do that to a limited extent, but not as a basic priority.

Just in terms of one concrete proposal, in the training of Ph. D. scientists like myself, which is paid for almost entirely from the public coffers, there is no component of the educational process that connects us up to health policy problems, and yet training grants are awarded competitively to universities on the grounds of what kind of training they can provide to their biologists, biochemists, microbiologists.

I don't see why the National Institute of Health, in looking over these competitive applications, can't expect a university to have a graduate course on, for example, the relation between biomedical research and health policy. Why shouldn't molecular biologists, biologists like myself, know something about what people in the country are sick from? What kind of a disaster could that be if we just took a couple of courses over 5 years in studying ill health in the country? Why shouldn't we have studied those cases where biomedical research was successful in solving health problems and in those cases where it failed?

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Then I looked at who was on this committee, and I found that Patrick Haggerty, the chairman of the board of Texas Instruments, the chairman of the board of Turner Construction Co., and president of the Digital Equipment Corp., *et cetera*, *et cetera*, were on the committee, and I looked for representatives of environmental groups. No, they weren't on there. I looked for representatives of consumer groups. They weren't on there. I looked for representatives of labor unions, of the people who were getting poisoned in plants. They weren't on there.

Then I understood why our policy on chemicals and health was a total whitewash, that the conclusions said something about regulatory procedures, and balanced regulations, balanced decisions, and balanced regulatory action, rather than calling for a major attack on chemicals, ill health, and the environment.

Now, I don't think there has ever been a congressional discussion that said,

> These are the problems of health in the United States. We have a major problem of ill health due to chemicals. Therefore, we are going to identify this as a problem, do biomedical research, and reassess 5 years from now, and the major thrust should be in that direction, *et cetera*, so that you could have a defined policy, get arguments on it, get input on it, vote against your representative because you could vote he took an unproductive stance on research policy, et cetera.

We just have a policy that says, "Go ahead with research." But go ahead with which research?

Mr. THORNTON. The point is, I think, that you are saying that the national research policy which is in place now needs to be modified or changed, rather than that there is no policy.

Dr. KING. Yes, that's right.

Mr. THORNTON. I wanted to clarify that.

I also would like very quickly to brush past one point you made, which I think might also deserve some additional discussion.

You said that there was no such thing as a compromise on safety, and perhaps in an ideal world that might be correct, although I am not sure that attaining a world in which complete safety existed would be an ideal world. I think that, subject to some question as to what is the ideal world, there is, in fact, compromise in the real world.

The balancing of risks against benefits is what we must actually do, in a practical sense, from day to day. Sometimes those balancing processes do not lead to the conclusions which I would like. For example, the American public has balanced risk against safety in tobacco smoking, and I didn't mean to illustrate this by referring to any members of the panel, but still the acceptance of that risk is a judgment on the part of the people who are involved.

Do you have any further comment with regard to that, Dr. King?

Dr. KING. Yes. I would like to make two points.

One, tobacco, and I would like to be very explicit about that. If you pick up the list of public advisory groups at the NIH, which the Government Printing Office publishes every year, you can look up the Committee on Biology, the Committee on Genetics, and you can look up the Tobacco Research Council, and this Committee is charged with research policy on lung cancer and cigarette smoking, and if you look at the panel, that is one of the few panels in the NIH in which half the members are representatives of the tobacco industry.

There was a time a couple of years ago when there was a water problem in Los Angeles when I was living there. There's still a water problem in Los Angeles. At that time I was working for the National Science Foundation on a microbiological expedition in the Antarctic, as a matter of fact, and there were a bunch of scientists who decided that they would turn their fancy training to the water problem, and they said, "Look, up there in the Arctic there's all that ice. All that water is going to waste, while down here in Los Angeles we're bone dry. Why don't we blast out a few icecaps, a few icebergs, and float them down to southern California and we'll have a water supply?"

They understood that this might have climatic effects, so they did a whole bunch of calculations, and they concluded that it wouldn't change the heat balance of the Earth to get rid of that white stuff that reflects the sunlight. It's very important in keeping the Earth's temperature steady. They said, "Well, let's do it," and some of us said, "No. We don't want you to do it." They said, "What are you, against progress?" "OK. Let's do it. We'll show you that there's no problem," and we said, "We don't want you to do that because if you're wrong there's no going back. We'll just be happy; we'll stay a little dry."

I think genetic engineering is the same thing. If the other side is wrong, we're in trouble. If I'm wrong and if Mr. Wheeler is wrong that we should slow and even hold off, it's no great disaster. Going slow is safe, but going fast can be disaster.

Mr. THORNTON. Mrs. Taft.

Mrs. TAFT. I would like to support the statement made by Dr. King just a few minutes before about investing our resources in appropriate channels.

I find it rather irreconciable to think that we are spending valuable money and time and energy to develop bacteria that will eat up the oil spills, instead of just preparing reasonable tankers that won't spill the oil.

Mr. THORNTON. You are aware, Mrs. Taft, that it was not recombinant DNA research that produced those bacteria, but that the bacteria had been selected through ordinary genetic means other than produced with recombinant DNA techniques are you not?

Mrs. TAFT. Yes. Natural, "in vivo" recombination. I mean it involves recombination, of DNA among different strains of a species.

Mr. THORNTON. I just thought the record should make it clear.

Mrs. TAFT. Absolutely. But the fact is they are now in the processes of testing these organisms as to what effect they would have if they survived in seawater and their effect on the environment, and all that energy and testing their survivability and effect.

Mr. THORNTON. If I may interrupt?

We were advised earlier that experimentation on that had been stopped. Can you comment on this point?

Mrs. TAFT. There was a lecture at Princeton this week which discussed this issue.

Mr. THORNTON. Our subcommittee was advised earlier during the hearings that this particular experiment had been stopped because of general concerns which had been expressed, which I share. It was speculated that these organisms might get of of control and we might wake up in the morning and find the automobile tank full of petroleum

people of varying backgrounds, interests, and concerns are involved in making those basic recommendations and policies, then it sometimes becomes a farce. There are self-interests that operate.

I'll take one of the fears that's expressed—and not too many people express it because most don't know what the recombinant DNA potentials are, or what it's all about. This fear is that there are some people who, because they are poor or because they belong to a minority, speculate that sometime in the future, not next month or 6 months from now, but some years in the future, a conscious decision may be made, for one reason or another, genetic engineering will be used to manipulate their lives. I feel that those people have a right to know and to help in shaping decisions.

We're having all kinds of lawsuits now stemming out of various drug treatments like diethylstilbesterol based upon the long-term effects that were not anticipated. Furthermore, I think of an example that sort of keeps recurring to me as we talk about what can and can't happen. It's the whole field of antibiotics. I suspect we've been having antibiotic actions for years, and years, and years, both in nature and in humans, and on plates that we cultivate in the laboratory. But nobody knew it. That probably was going on unrecognized ever since we ever understood anything about microbiology, until one day one scientist asked, "What in time is that?" Now, it could very well have been not the beneficial thing that it turned out to be, but a very harmful thing to society, that was going on year after year after year.

So I believe we have to reach compromises. But our basic concern, and I think I hear Dr. King saying that maybe we shouldn't be doing this research at all, therefore I doubt if there's a compromise possible for him. It's more perhaps out of desperation, ignorance, or whatnot, but we have to admit, genetic engineering is here and ask what do we do with it?"

Mr. THORNTON. Thank you, Mayor Wheeler.

One of the anachronisms of our Federal regulatory pattern may be noted in the varying actions of Government with regard to diethylstilbesterol—this particular hormone is being reexamined to determine whether it should be banned as a feed supplement for cattle because of a suspicion that it may be carcinogenic and because it may persist in a very, very small quantity in the livers of the cattle which is eaten by humans. The anticancer clause of the Food, Drug, and Cosmetic Act prohibits the use of any substance which remains in food and which is carcinogenic. And yet, the same hormone has continued to be marketed as a drug for direct use by human beings. I've never quite been able to understand that anachronism although I recognize there are differences in risk/benefit analyses between drugs and animal feeds.

I also would like to comment, before asking Dr. Krimsky if he has any comment at this time and before turning to other members of the panel, on your suggestion that because of the stage which the research capability and knowledge has now achieved that it is possible that regulation, unless it is at least national and probably worldwide in scope, might result in a kind of Gresham's law by which unrestricted research would drive out the restricted research, and the areas of the world with no research regulations would continue to perform the experiments restricted in the United States.

have not been the resources available to really control and investigate this whole problem.

Mr. DORNAN. The reason I ask is that all of you have expressed a concern about regulation being recommended by those who weren't worried about the regulation and see no need for it. I think this is one of the principal problems here in the Congress of the United States; deciding whether the networks should regulate themselves, or whether the motion picture industry should regulate its own level of sex and violence, whether or not the oil companies should regulate themselves, whether oil tankers should decide their own safety laws.

And if the public is so apathetic about an epidemic, where we know the cause, and it isn't scientists just sneezing in labs doing research on gonorrhea or syphilis, then I see real danger here for the public being totally bored with this DNA research. If there isn't some inside concern by scientists who are worried about this, then there won't be any regulation at all if it's coming from people who just say, "Plunge ahead. Push back the frontiers. Who cares?"

Mrs. TAFT. It's going to be very difficult because the people who are actually working in it have an inherent resistance to regulation. There is this very nasty picture of a Federal inspector coming in and snooping around a laboratory without really knowing exactly what is going on, and it is true that you can't just send somebody who has a list of things that he has to check. There needs to be checking for the use of the nontransmittable plasmids, which are ruled in the NIH. You have to check that enfeebled bacteria are being used where they ought to be. Without it, we have no safety. It becomes a risk, even by definition of the drafters of the NIH document. There is going to have to be scientist involvement in the enforcement procedure by other scientists. Perhaps one could envision the Federal Government being involved in assigning different laboratories to check other laboratories and signing a Federal statement to the truth, to the effect of that.

But if people understood a threat to them, I think that they would become awake from their dormancy, as I think has been the case in the nuclear developments.

Mr. DORNAN. May I ask Dr. King a question, because again, this is certainly a major problem.

Where do the regulators come from? I sit on another committee, Merchant Marine and Fisheries, where we have observers going out to the fishing boats, and they're certainly not fishermen and they're certainly not seamen generally, and it's not a Federal job requirement, but they think it would be fun to go out on a tuna boat, and the captains deeply resent it.

But then there seems to be a need on some boats for an observer.

What is it, Dr. King, that impels one scientist to develop this awe of this particular field, of DNA research, where he would be going against what I would think would be the normal scientific impulse to push back the frontier, that curiosity that compels a young man or young woman to go into science in the first place. What causes one scientist to say, "Look, go slowly here," and another scientist to say, "Well, let somebody else worry about that. I'm pressing ahead just as fast as I can in my brief lifetime."

Dr. KING. I think it comes out of previous experience, and I think this is very relevant to the question of regulation.

clear to me that the Secretary of HEW should not have the power to regulate recombinant DNA, that it should be in EPA, and yet I don't know how to prevent the war between those two agencies. That, I think, Congress has to deal with.

Mr. DORNAN. We've certainly moved into a generation of science, and I think it's going to have to come from the scientists themselves, this role of leadership on how to move very slowly in these dangerous areas.

As fascinating a person as Adolf Hitler is for a psychological study, and you can't get very far into DNA discussions without touching on the German experience, I've never found him as fascinating as scientists and doctors of mature, middle years who use that period to engage in diabolical experiments on other human beings, and many of them have just disappeared into the woodwork after the regime collapsed, and it appears that, after a trip to Washington, D.C. 2 years ago, when I witnessed a panel of doctors, one of them literally pounding on the table for the right, as he called it, to strip the flesh of living fetuses and use it in bird research, I realized that we're not very far from the middle 1940's in scientists demanding unlimited rights to do whatever they decide is proper at any given moment.

So I appreciate scientists coming forward, and I wish in other areas that we had oil men with the same concerns and fears about tanker spills because a tanker spill may be tolerable, a small one, in a horrible energy period, but a sneeze of a scientist coming out of a laboratory in this type of research is totally intolerable.

Thank you very much.

Dr. KING. I was asked by people at Cambridge to bring a few requests here.

One request was that financial support be made available to those groups who are trying to put together material for this research.

[The material supplied by Dr. King is as follows:]

The **Genetics and Social Policy Group** was formed in response to recent attempts to trace societal problems to the genes of individuals rather than to inequities in society itself. The group successfully challenged research on the relationship between chromosome abnormalities and "deviant" behavior at Harvard Medical School and elsewhere.

The group has been concerned with the health hazards of DNA-recombinant work since the beginning of the controversy. Articles, position papers, press releases, criticisms and suggestions have been distributed to both the scientists, who have been making the decisions concerning this work, and the press. On a grass-roots level the group has attempted to help organize clerical workers, lab technicians, custodial staff, graduate students and other people at risk into safety committees, which can confront the dangers to health that DNA-recombinant and other laboratory work presents.

The group has also written pamphlets (*Genetic Engineering* and *Race, I.Q., and Genetics*) and magazine articles for *Psychology Today, New Scientist, Science Teacher,* and *Science for the People.*

Correspondences concerning this pamphlet, the **Genetics and Social Policy Group,** or **Science for the People** can be directed to the Science for the People main office at the following address:

SESPA/SftP
16 Union Sq.
Somerville, Mass. 02143
Tel. (617) 776-1058

Cover picture: Electron micrograph of a male and female cell of *E. Coli* connected by *F. Pili* (possibly exchanging DNA). Photograph by Lucien Caro (x46, 200).

Experimenters claim the ultimate justifications for this work are potential applications in agriculture, industrial processes, and medicine; inserting nitrogen-fixing genes into non-leguminous plants so that they would no longer require nitrogen fertilizers, constructing novel strains of bacteria to eat up oil spills, and correcting genetic deficiency diseases. These rare genetic defects such as hemophilia, thalassemia, sickle-cell anemia, and alkaptonuria might someday be correctable by genetic surgery, although we doubt the wisdom or desirability of such eugenic therapies. The role of genetic arguments in distracting attention from the much more important social and environmental determinants of ill-healths is described elsewhere.[3] Here we simply note that scientists are pursuing these genetic technologies primarily for reasons unrelated to public health or other social needs. In the past allowing scientists the freedom to pursue the experiments they chose has not been a great danger to human health, but this may constitute just such a danger in the future.

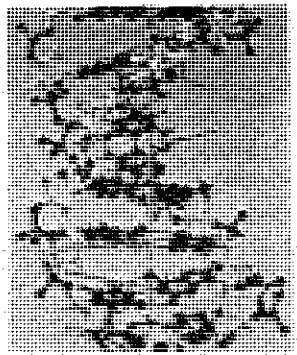
Before describing the dangers, we will briefly discuss the elements of gene transfer technology. Genes to be implanted in *E. coli* are first cut from the whole DNA molecule (a gene is a stretch of the DNA) by purified "restriction enzymes" and are then added to a test tube containing a solution of a small section of *E. coli* DNA (a 'plasmid'). Because of their molecular properties the donor implant gene and the *E. coli* plasmid DNA loosely associate into a new continuous chain, whereupon another added enzyme chemically seals the implant in place. The result is a new *E. coli* plasmid DNA molecule indistinguishable from its initial state except for the addition of the newly implanted gene. This new plasmid is absorbed by the baetaeria, the genes are "expressed", they multiply, and they can be transmitted from bacterium to bacterium.

In this pamphlet we will focus on the public health hazards of creating these unnaturally altered organisms that transgress natural species boundaries and the powers of evolutionary control. Because only a few people stand to benefit from gene implantation, although many are at risk, we need an adequate amount of time to assess the risks. Any social benefits of gene implantation which may arise will be of equal value whether they arrive in 25 versus 20 years, or 105 versus 100 years. For five or ten years now a slow, thoughtful research-based approach to limit the hazards makes sense.

HISTORY OF THE CONTROVERSY

Before describing the dangers it is worth reviewing the form the controversy has taken. A small group of molecular biology research directors in July, 1974 addressed a letter to the scientific community and explicitly asked that all research on "recombinant DNA" molecules (gene implantation) stop until the risks involved and safeguards necessary to conduct the research were evaluated. These scientists acted laudibly in displaying concern about possible undesirable consequences of their research. Scientists have rarely accepted responsibility for the destructive consequences of their work.

A group consistaing predominantly of research directors was expressly invited to attend a meeting at Asilomar, California, in February, 1975 where these questions were discussed. A resolution representing the consensus of the meeting was adopted suggesting research guidelines and calling for the establishment of a committee under the auspices of the National Institute of Health. This committee would be empowered to draw up a system of safety and containment procedures, and of recombinant DNA recipient organisms to be used in these dangerous experiments.



at the U.S. Army Biological Laboratories at Ft. Detrick, Maryland, alone. What will the casualty list look like when there are hundreds of laboratories conducting such experiments?

In the next most stringent class of physical containment facilities there is already evidence of inadequacy. A research director reported that within a year all workers in his laboratory exhibited a positive reaction for the biological agent that was supposed to have been contained.

Physical containment standards should be more than just sufficient. In the real world apathy, carelessness, pressure, and faulty or inadequate apparatus lead to breakdowns in containment. Most scientists agree that a physical containment system should be secondary to a "foolproof" biological containment system. Although the probability of the crippled bacteria escaping from the laboratory is small, it is not zero. In theory only those bacteria which have an ontside survival probability of less than one in 100 million could be used as gene implantation recipients. But a one quart laboratory culture of *E. Coli* may contain from 10-100 million bacteria (the amount of *E. Coli* that one laboratory worker might use in one day). On this basis, thousands of bacteria which are capable of existing in the outside world already exist in that culture! It is possible, through positive adaptation and preferential selection, for the survival potential of a bacterium in culture to be radically increased by a single mutation in its DNA.

A further complication is the possibility of genetic exchange from the crippled bacteria to stronger, healty strains which can survive in the outside world. This could happen for example on laboratory surfaces in the event of an accident, or similarly in the human body following ingestion or inhalation, or by contamination of the crippled culture with faster-growing healthy strains. Moreover there is evidence that genetic transfer could occur even after the death of the crippled host. In this instance a dead bacterium may be almost as dangerous as a live one. Although such events are unlikely, over many years they become a distinct possibility.

E. COLI CAN ALSO BE HAZARDOUS TO YOUR HEALTH

For the two reasons stated above, (1) that *E. coli* freely inhabit humans, and (2) that these bacteria are extremely adept at the exchange of genetic material, possibly the worst choice for a recipient of gene implants has been made. *E. coli* has been chosen because of convenience to experimenters, not public safety: Another recipient could be developed which is much further from the human biosphere than is *E. coli*. If the committee truly had the interests of the public at heart it would have insisted on a recipient much more remote from humans.

The cold facts remain that the proposed safeguards have not been validated. In view of these uncertainties it would seem safe and prudent to proceed with only what are generally agreed to be the less dangerous implants. If the containment facilities prove satisfactory, then perhaps more dangerous experiments might be attempted. This is just good scientific practice. As the guidelines now stand, however, virtually any recombinant DNA experiment can be performed. This reckless assumption that all experiments should be possible at the present time seems to contradict the spirit of Asilomar as exemplified by the statement of committee chairman DeWitt Stetten, "... that if something had any probability at all, it would in all likelihood occur, and that this should be a guiding principle of our deliberations."

What then are the real dangers of these artificially constructed bacteria? The answer is somewhat rhetorical as well: we don't really know. This along should be cause for trepidation. It would be easy to construct horror stories about bacteria gone berserk, or powerful biological toxins implanted into the genes of ubiqnitons human-inhabiting bacteria thus constructing novel biolobical bombs, etc. This is not unheard of, one only need recall the 1972 London smallpox outbreak, which oraiginated in a research laboratory. For every fairy tale which ends with, "And they lived happily ever after," an equally disasterous scenario can be painted.

It would be highly desirable, for example, to construct a bacterium in which the genes for insulin biosynthesis had been implanted. Such bacteria could supply insulin cheaply in virtually unlimited amounts. However insulin in greater than minute amounts is a deadly poison, and were *E. coli* harboring an active for insulin biosynthesis, to gain admittance to human intestinal tracts, the results could swiftly be fatal. Here then is a highly desirable candidate for gene implants, all the more so being a potential financial boon, which could easily have undesirabled consequences. The pharmaceutical industry would be extremely interested in constructing an insulin producing bacterium. However containment problems on a large industrial scale are compounded enormously. Industrial vats will replace academic test tubes. Historically the health and safety of the American worker have not been of prime concern to American industry, nor in academic or scientific circles for that matter. Will



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BENEFITS OF GENE TRANSPLANTATION RESEARCH

In order to evaluate the risk-benefit equation for gene transplantation research, it is important to determine just what the real benefits are likely to be, and to whom these benefits will accrue. Since it is society at large that provides the funding and runs the risks, it is clear that benefits accrueing to the general public are needed to justify this research. If the benefits to society are small, then this research should not proceed. The proponents of this research seem to recognize this, and do indeed promise great rewards for mankind. Is this promise likely to be fulfilled? And, if so, who is to decide that these benefits are worth the risks?

The proponents of gene transplantation research suggest benefits to the general public in several different areas: cheaper biologically active chemicals (e.g. insulin and antibiotics) for the treatment of diseases, increased food production, and a greater understanding of disease processes. Let us assume that the technique can be usefully employed in each of these three areas and ask who benefits.

Cheaper Biologically Active Chemicals for Treatment of Disease

When one speaks of the promise of cheaper insulin and cheaper antibiotics, one is making the assumption that these materials are now expensive to produce. But that is not the case; these drugs are already being produced at only a few cents per dose. Of course, the consumer pays much more, but this reflects not the difficulties of drug production, but rather an industrial structure in which secondary costs such as extravagant packaging, advertising, and profits to the few inflate the price to the consumer. Is it being seriouly suggested that if these same companies are given a method of producing drugs at a slightly lower cost they will pass on significant price reductions to the consumer?

Increased Food Production

The insertion of the genes for nitrogen fixation into non-leguminous plants or into the bacteria normally associated with the roots of non-leguminous plants is said to mean more and cheaper food. Here also there are unstated assumptions. It is assumed that food costs reflect the high cost of nitrogen containing fertilizers and that the scarcity of food, especially in the underdeveloped world, reflects the inability of the farm sector to keep up with demand. However, the world-wide shortage of food would seem to reflect more the deliberate restraint of production in order to keep world food prices high than the world's inability to produce sufficient food. The results of the Green Revolution are enlightening on this score. In that circumstance high yield rice strains were developed and distributed, but it was only the already well-to-do who could afford the additional costs of the cultivation they required, and the end effect was to worsen the plight of the subsistence farmer.

Greater Understanding of Disease Processes

Finally, who will benefit most from a greater understanding of cancer and genetic diseases? What the general public needs, much more than a detailed understanding leading to cures, is an understanding leading to prevention. The path to prevention of cancer is already clear: eliminate our exposure to environmental carcinogens in the workplace and home which are the direct cause of the vast majority

P3 and P4 Levels of Containment

P3 and P4 containment are as equally if not more so deceptive in terms of what they actually contain. In truth, they represent psychological containment, i.e., they are a continual reminder of the dangers involved to the laboratory worker. In truth also, they in no way can guarantee containment of micro-organisms. This is the case despite negative pressure facilities, limited access laboratories, airlocks, etc. It is well documented in the report written in January 1976 by Dr. A.G. Wedum, M.D., entitled, "The Detrick Experience as a Guide to the Probable Efficacy of Microbiological Containment Facilities for Studies on Microbial Recombinant DNA Molecules." This report, based on 30 years of containment experience at Fort Detrick, states that neither P3 nor P4 facilities can guarantee absolute containment. It further concludes and suggests that for such potentially dangerous research two conditions should first be met: 1) a safe (noninfective strain, one which cannot infect or transfer genetic information in the human population) strain should be used; and, 2) a vaccine against this strain should be made. No vaccine is being prepared presently and this in itself is almost an impossibility (because every newly transplanted gene can affect the properties of E. coli and therefore make it resistant to any vaccine; thousands of different and uncharacterized genes from hundreds of different organisms are now being genetically transplanted into E. coli). With respect to the first suggestion-- the construction and use of a safe strain-- no such strain exists at this time. Efforts have been made to construct one, but it has not been so certified and will not be so certified in the near future. Furthermore, this effort to construct a safe strain, which has not succeeded, is only an effort directed towards making a theoretically safe strain (i.e., an EK-2 strain). The Wedum report spoke of another variety of safe strain-- one which has been tested in humans (i.e., an EK-3 strain)-- and this is at least another 5 to 10 years off in construction and testing.

Considerations Concerning Dispersal of E. coli

It can therefore be concluded that at present, no facilities exist which can guarantee absolute containment of work with recombinant DNA molecules. It should also be noted that the major vector for the spread of this work will be the laboratory personnel themselves. They will surely be contaminated with the genetically manipulated E. coli they work with. And they will most certainly, despite air-locks, negative pressure facilities, etc., etc., carry these organisms out of the facilities either in their gut or pharynx or on their skin and clothing. The organism host in question, E. coli, infects all warm-blooded animals. It is also found in the gut of insects, birds, and fish. It also can be found in rivers and oceans, on grass and on vegetables. It is airborne and can also be spread in water. E. coli is an incredibly sexy organism-- it carries on the conjugal act for over two hours, and it can exchange genetic information with all other species of E. coli and some non-coliform bacteria. It matters not whether the organism will lyse in the gut or colonize the human gut. Transformation of naked DNA has been known for many many years and attachment of genes to plasmid only increase the likelihood that the newly implanted genes will be spread to any one of an almost unlimited number of eventual hosts. This in turn is only compounded for the worse since there is absolutely NO way to monitor for the escape of these microorganisms or their genetic implants. Furthermore, there is no way to even predict where they will end up, what their expression will be, or how long this will take.
Two out of every 1000 patients who enter Boston hospitals die from E. coli infections (New England Journal of Medicine, 1976). Are we to add to this toll?

BIOLOGICAL CONTAINMENT

The proposed NIH Guidelines (January 1976) are a set of proposals that attempt to contain bacterial hosts and/or viruses carrying implanted foreign genes by a combination of different levels of physical and biological containment depending on the particular experiments to be performed. Biological containment refers to the use of genetically modified or "weakened" strains of the human gut bacterium Escherichia coli as hosts for the introduction and propogation of foreign genes. This strain (which the Guidelines refer to as EK-2), it is hoped, will "...not permit survival of the cloned DNA fragment in other than especially designed and carefully regulated laboratory environments at a frequency greater than one in one hundred million ($1/10^8$)." (1) In practice, the difficulties to obtain and assess a particular level of biological containment are many.

Dr. Roy Curtiss III and eight co-workers at the University of Alabama in Birmingham have worked for the past 1½ years on the construction of a weakened strain of E. coli. They have recently presented a thorough and candid account of their observations of that strain to the NIH Committee which is presently considering it for certification as an EK-2 strain. Curtiss' group has pointed out that the reduced survival of the strain they have constructed cannot assure reduced survival of the strain carrying a foreign DNA fragment. In general, in order to insure reduced survival of the strain carrying a cloned foreign DNA, the number of strains to be tested would be enormous given the number of different DNA fragments possible for implantation into E. coli. In particular, it would be only logical that the Guidelines demand that every strain carrying a new DNA fragment be tested under the most stringent conditions of containment, at considerable expense both in terms of time and money.

Obstacles to Containment

Other obstacles will diminish, and not unlikely, eliminate the possibilities for the biological containment of any E. coli strain:

1) The occurrence of genetic exchange from the constructed "safe" host/vector to other strains of E. coli commonly used in the laboratory. Bacterial and viral contamination of laboratory cultures is very common in microbiology laboratories, despite extreme precautions taken to prevent contamination. Implanted DNA could, by virtue of genetic exchange, find itself in a bacterium that is able to survive under much more varied conditions than its original host. Considering the converse situation, a routine laboratory culture of E. coli contaminated by the "fail-safe" organism harboring a DNA implant could provide for entry of the foreign DNA into a large bacterial population. This situation is not far-fetched, considering that "routine" cultures are ordinarily discarded into open sinks.

2) It is a common experience that multiply marked strains (strains carrying a variety of genetic mutations differing from the wild-type bacterium) are very difficult to maintain. It is hard to imagine that every laboratory worker using the weakened strain will insure, prior to each experiment, that the particular strain being used maintains the original 13 or so mutations that, say, the strain constructed by Curtiss and co-workers contains. The thoroughness demanded of any experiment in microbial genetics, let alone foreign gene implantation, would require testing for the 25 phenotypic properties that the above mutations confer to the strain.

3) Given how little we know about the ecology of ubiquitous E. coli, we will involuntarily ignore many situations in which this bacterium could be tested for survival. The number and variety of natural environments that can be tested is only limited, for one example, by the different compositions of the sewers receiving effluents from the hundreds of institutions in which DNA

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there is no comparative epidemiological study that assesses the incidence of gastrointestinal infections and urinary tract infections (in men as well as in women) among people working in microbiological laboratories versus groups of people outside of laboratories. To our knowledge, there is no study that has assessed the incidence of meningitis and infantile gastroenteritis in young families of laboratory workers. To our knowledge, there is no epidemiological study that has assessed the incidence of prematurity and perinatal mortality in infants of women working in laboratories or their close female associates.

Conclusion

Only formal and detailed epidemiological studies can fulfill this lack of knowledge. Chemical pollutant studies offer sobering examples to this effect. It has been recently demonstrated that a sample of wives of husbands who came in contact with vinyl chloride had twice as many miscarriages and still-births as the wives of workers who did not come in contact with the material (3). This occupational health hazard probably would go unnoticed were it not for the depth of the study conducted, which was made imperative in light of the discovery that vinyl chloride is carcinogenic to humans.

Proposal

General concern about the potential health hazards of DNA implantation techniques (not only to people, but also to a wide variety of other species) would demand postponement of this line of experimentation until at least the above uncertainties, as well as those concerning physical and biological containment, are experimentally resolved. This would involve a substantial redirection of effort of the biomedical research community into detailed study in the areas of occupational and environmental health and safety. An agreement among the scientific community not to make use of the potentially threatening technology of DNA implantation into microorganisms would circumvent this problem. We should seriously consider the use of alternative technologies which might be considerably less costly and disruptive of daily laboratory life than the construction, maintenance, and monitoring of P3 and P4 facilities and "safe" hosts. An alternative approach to gene implantation would also eliminate the process of decision to continue genetic engineering research based on benefit versus risk calculations, simply because the risk, at least as it has been posed by the molecular biology community at large, will be negligible.

Proposed alternative approaches will not interfere with the attainment of knowledge that DNA implantation seems to promise. It may slow the acquisition of that knowledge; however, most likely it will introduce the kind of patient wisdom into the process of scientific research that large segments of society are beginning to demand. It remains an open question whether scientists, left to their own devices, are capable of the collective restraint which is a prerequisite to that kind of wisdom.

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I. INTRODUCTION

1. Position of Science for the People

This paper represents the position of the Group on Genetics and Social Policy of the Boston Area Science for the People. For over three years our group has been active in raising questions about the social implications of research in genetics, in genetic screening, and in gene implantation.

2. I am newly conscious of political responsibilities

I speak as one newly awakened to the responsibilities and privileges of scientists. I should say reawakened, because somewhere in the back of my consciousness lay the memory of personal but barely articulated guilt about the construction of a bomb.

My parents suffered from a major ambivalence: having worked on the Manhattan Project, they felt personally defensive about the horrors wreaked by the results of their research; but this concern was not sufficient to overcome the notion that the scientific endeavor is the main avenue for the pursuit of knowledge and that, therefore, scientists have special privileges.

3. The responsibilities of scientists: Pure research and the choice of research projects

There is a common belief that scientists are not responsible for the repercussions of their work. This follows from the belief that scientists should follow their research wherever it leads them, and that they should be free to do this. The rationale for this belief is that pure research could lead to great and useful discoveries, that outside controls would inhibit progress and turn science into a political tool, and that, since scientists are made pure by their commitment to the pursuit of knowledge, such control should be superfluous.

Though this sounds a bit simplistic, we know that many scientists and much of the rest of society would like to believe it. (In fact, I myself believed it until very recently.) Nevertheless, the direction of our research is already

tainly be so now. I have wondered at what seems to be the light-hearted attitude of so many respected biologists about the prospect of transplanting genes across species barriers (3, 39, q41).

The results of our research have direct bearing on the public welfare. It has been pointed out that there are both potential hazards and potential benefits. The benefits are often painted in such an exaggerated fashion that many of the informed public and, indeed, many biologists have come to believe that this technology will save the world from disease and starvation. (Of course, equally exaggerated scenarios of disaster can also be imagined.)

2. Scientists are not the appropriate judges of the legitimacy of this research; the public is at risk

We as scientists may be best suited to calculate risks and to predict benefits, but does this mean that we are best able to decide whether or not to run the risks? It is here that the debate becomes one of public policy. A small number of scientists in influential positions should not have the power to shape the future. It is the public which is at risk, the public which should benefit, and the public which should decide whether the benefits justify the risks.

3. Anyone can understand the issue

With few exceptions, the public is not in a position to make decisions about scientific matters due to the lack of social mechanisms to allow for public participation and to the mystification of the scientific endeavor which pervades our society. This, in turn, is due to an elitist attitude promulgated by academicians that only a few people are capable of higher learning. I do not want to debate this issue at length; however, my own experience is that anyone can understand the issues that we are discussing here, and can ask probing questions which are difficult to answer. Because this research has such impact on society, it is our responsibility to educate the public and to

cult, global problems raised by the research.

6. The Guidelines have not been available to the public

When the Guidelines were released, they were sent to major investigators, editors of scientific journals, and the like. Especially in the light of the public interest which had been displayed by news coverage and local city actions, why was no effort made to make the Guidelines accessible to the general public? They should have been distributed, complete with explanations and an expanded glossary, to every public library. At the very least, the Guidelines should have been made immediately available to science libraries so that interested and informed individuals not directly involved in the research would have easy access to them.

7. The environmental impact statement should have come earlier

The handling of the environmental impact statement for the Guidelines provides further demonstration of how public access has been limited. Publishing a Draft Environmental Impact Statement before issuing the Guidelines would have been in keeping with the spirit, though beyond the letter, of the National Environmental Protection Act. However, it has finally emerged two and a half months after the Guidelines. As required by law, time was allotted to receive public response but a member of our group found that the month provided was inadequate even to obtain a copy of the Draft on request.

8. The use of language is important

Even the language we use is important. Recently, I asked a friend who is trained as a philosopher of science whether he would read an article in the New York Times about recombinant DNA. He doubted that he would, but said he would certainly read about Transplanting Genes which, after all, is what this is all about (8).

When Dr. Fredrickson of the NIH speaks of the potential dangers and the promise of great benefits (39, q12), the bias of his viewpoint is clear. It is not clear to us that the benefits are any more likely to be realized than the dangers. What is clear is that, since there is potential danger of a disastrous and irreversible nature, the decision to continue this work is not the scientists' alone.

9. The consequences of this work are not predictable

An enlightened view held by many people has been well articulated by Prof. S. E. Luria:

> I personally believe that not all research is legitimate: its legitimacy has to be judged in terms of its clearly predictable consequences (23, q24).

We would go a step further. One cannot predict with confidence the consequences of research in Gene Implantation. Under such circumstances, what is needed is a careful analysis of the possibilities. Even when one cannot easily assign probabilities to the projected consequences, if significant hazards can be projected it becomes absolutely necessary to open up the decision-making process to the public. We must not allow the natural bias of those involved in the research to predetermine the decision to proceed or not. Since it is impossible to be free of bias, the only way to allow the public to make balanced decisions is to make our biases known and explicit.

10. We cannot be free of bias

We do not mean to imply that it is only when the scientific questions cannot be answered that the public need be involved. It is often true that, even when the scientific implications are clear, there are moral and political

make the decision a shared one.

4. The debate has not been public

It is often said that an attempt has been made to open the debate to the public. The examples that are generally given are the Asilomar Conference, which was reported in many newspapers, the NIH hearings in February of this year, which were called "Public Hearing", and the NIH Guidelines, which are supposed to open to public scrutiny and criticism. We question the public nature of these forums. The fact that the Asilomar Conference was convened by inviting a group of prestigious individuals without extending an open invitation to interested persons from the general public is indication enough of the semi-public nature of this forum (44).

5. The experts should not be only molecular biologists

There are obvious problems involved in making the NIH both the funding agency for the research as well as the body responsible for its regulation. In addition, why was the NIH Guidelines committee so heavily staffed by molecular biologists (41, q3, 4)? It is quite true that there were important technical questions that needed to be addressed in order to propose the Guidelines. Some of these involved the details of how the experiments would be done and, in this regard, the molecular biologists planning to do the experiments were indeed the appropriate group of experts to be consulted. But the much thornier, and more important, scientific questions are those of danger to public health and to the biosphere. Evolutionary biologists, ecologists, epidemiologists, infectious disease experts, and public health officials should have been on the committee in force in order to deal adequately with these aspects of the application and repercussions of the research. Remember, too, that not all of the questions raised by Gene Implantation research are scientific in nature; there are moral and social dilemmas to be confronted as well. Philosophers and historians of science should have been present to assure careful consideration of the diffi-

guided by outside pressures: the limitations of the budget, the priorities of the funding agencies, and the constraints imposed on them by societal interests such as public health, and by social and ethical considerations such as the restrictions on human experimentation (5, 23, 36).

How can we claim that scientists can choose what to study when it is clear that the granting agencies, variously persuaded in Congress, do a large part of the choosing? Also, professional pressures encourage us to investigate currently fashionable subjects; not to do so would jeopardize our chances for success and more grants.

Most scientists seem to believe that science somehow hovers above the social fabric; but, if science is at all pure, it is only in the search for new knowledge. As long as society uses the products of science, science cannot be neutral because social actions are always moral issues (23, q24). There is no value-free science. Though some view science as entirely objective, many associate only a positive value to science, and see its applications through rose tinted glasses. They do not recognize that, without careful planning and forethought, science can lead to disaster as easily as to advantage.[1]

II. POLITICS AND PUBLIC DEBATE

Let me ask bluntly: Should we pursue the study of recombinant DNA? If we should, under what circumstances? And who is to decide?

1. Many biologists are not worried about inter-species gene transplantation

We are indebted to Professors Berg and Baltimore and to the rest of the Asilomar Conference organizers for having first pointed out the need for caution in this field of research. Indeed, so much valuable time has been spent in discussing this issue that, had I not been concerned to begin with, I should cer-

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GENE IMPLANTATION:

PROCEED WITH CAUTION

A discussion of the hazards of research in recombinant DNA

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ON ESCHERICHIA COLI AS HUMAN AND ANIMAL PATHOGEN

There is considerable evidence that E. coli, under certain sets of presently ill-defined conditions (in certain cases, when carrying certain extrachromosomal genetic elements called plasmids) can be a pathogen to humans and other animal species, and is more pathogenic to younger members of these species. Much of this evidence has been gathered only recently. To quote a recent review, "During the past approximately six years, the recognized role of enterotoxigenic E. coli in producing human diarrheal disease has expanded to encompass a wide clinical spectrum, ranging from mild travelers diarrhea to a severe cholera-like illness and involving essentially all age groups, from the nursery to geriatric populations." (1) Diarrheal disease is one of the main causes of death in children under five years of age in developing countries and is an important cause of adult morbidity in the same areas (1).

In industrial countries, E. coli can also be harmful. Little is known about the mechanism of its pathogenicity as well as its mode of infection. Infections of the urinary tract are common in women of any age and are especially common during pregnancy (2). Infection during pregnancy leads to increased incidence of prematurity and perinatal mortality. Furthermore, E. coli is responsible for about one third of the cases of meningitis (inflamation of the nerve and brain linings) in neonates. Premature children are particularly susceptible (80-90%) to this infection (2).

Colonization Studies

Proponents of gene implantation utilizing the strain E. coli K12 as host have often argued that this particular strain is known not to colonize the human gastrointestinal tract. However, this strain was originally isolated for human faeces close to 50 years ago. It has been maintained in the laboratory, and presumably, according to optimistic opinion, has been divested of its capacity to colonize the human gut. However, this opinion ignores the observation that in most experiments on human volunteers, ingested E. coli strains (of a variety of different types) were either not recovered at all, or persisted in the bowel for only a short time (2). Little is known about the dosage of coliforms which must be ingested to significantly influence the population dynamics of the faecal flora. In other words, it is extremely difficult to know whether E. coli K12 does or does not colonize the human intestine. Furthermore, the factors enabling E. coli K12 survival and maintenance in the human urinary tract are not known. These uncertainties suggest that we cannot derive comfort from the negative reusults of the tests involving the administration of massive doses of E. coli K12. Drawing from the field of plant pathology, it is sometimes very difficult to experimentally obtain infection of a plant with large doses of an isolated microbial agent, even though the agent is known to diaperse throughout a crop under natural conditions.

Lack of Thorough Epidemiological Studies

Finally, the claim that E. coli K12 (let alone an equivalent strain containing foreign implanted genetic information) is not a pathogen under any circumstances has not been put to a rigorous test. To our knowledge,

implantation technology is proposed to be utilized.

Conclusion

The above considerations lead to the conclusion that the experiments assessing the properties and survival of the weakened strain (or foreign DNA carrying derivatives) will unavoidably be incomplete. Furthermore these assessments will not have been repeated by independent groups, a normal procedure before a crucial experiment is accepted by the scientific community. Clearly, the task to gain certain assurance of the efficacy of the biological containment of an E. coli host/vector system is staggering, and the dedication of enormous funds to test the wide and complex variety of conditions in which E. coli naturally finds itself would border on the absurd.

Proposal

A calm analysis of the above uncertainties facing genetic engineering research in general, and biological containment in particular, would prompt us to consider "alternative technologies", which are potentially less disruptive of microbial life in our pursuit to understand how genes function in higher organisms. It has been repeatedly maintained that the latter objective can only be acheived through the techniques under consideration. However, techniques other than cell DNA implantation already exist that have allowed the isolation of the genes coding for rabbit hemoglobin (2,3,4) and the gene coding for the silk protein of an insect (5).

Larger amounts of initially minute quantities of a particular DNA sequence could be obtained by the use of appropriate in vitro systems (for example, enzymes (polymerases and ligases) stably immobilized to solid adsorbents to allow for long-term continuous use) to achieve the replication of an initial DNA copy. A promising approach for the isolation of a large variety of genes starting with the isolation of their corresponding messenger RNA's is offered by the technique of immuno-precipitation. This method involves the precipitation of the messenger RNA-nascent protein-ribosome complex away from other cell components by use of antibody specifically directed against the native protein. Once the messenger RNA has been fractionated from the above mixture a complementary DNA copy can be elicited by incubation with appropriate available enzymes.

Techniques of this kind which will be presumably, at first, not as "easy" as those offered by insertion of foreign into bacterial host/vector systems could be coupled with a decision by the scientific community to focus on the study of a few genes from higher organisms. This enterprise would offer the kind and depth of detailed knowledge scientists wish to obtain earlier than under the present state of affairs, where, it would seem, every group has its "own" eukaryotic gene to study. There is precedent for an agreement of this kind. Seventeen years ago the molecular biology community and the granting agencies decided to concentrate the study of the regualtion of gene expression in bacteria to the genes coding for the lactose utilizing enzymes of E. coli. A similar initiative, utilizing alternative techniques to those offered by gene implantation technology, will permit our understanding of eukaryotic gene expression to progress without risking "biological pollution" in its deepest sense.

Ecological Implications

Some quotes for thought from "The Ecology of E. coli" by Dr. Stanley Falkow (1976):

1. "From the specific standpoint of the detection of E. coli host strains uaed for recombinant DNA molecules and their dissemination serotyping appears at present to be of no significant value"--i.e. they cannot be monitored!
2. "The natural habitat of E. coli is the alimentary tract of man and warm blooded animals."
3. "On the other hand, antibiotics used in therapeutic and subtherapeutic doses may have a profound effect on the normal flora, rendering the animal susceptible to infection by pathogens and enhancing plasmid transfer." The same conclusion, even more so, would hold for patients undergoing immunosuppressive therapy.
4. "From the standpoint of recombinant DNA molecules, the documentation of the effects of plasmid-mediated determinants on pathogenicity must be viewed as one of the most cogent arguments for the potential biohazards associated with this research."
5. "The 'indigenous' plasmid flora of E. coli would represent (at least in theory) a ready body of vehicles to mobilize and recombine with the laboratory constructed molecules under proper circumstances."
6. "It is also clesr from out studies that a carried plasmid may have a profound effect on the survival and carriage of E. coli K-12. As noted earlier, many E. coli can be converted into pathogenic form following the infection with Ent and K antigen plasmids." What effect will the thouaands of unknown genes from hundreds of different organisms have on the pathogenicity or nonpathogenicity of E. coli or any other bacterial strsin which these new gene implants are transferred to??
7. "Yet, it may not be too far fetched to suggest that some DNA recombinant molecules could profoundly affect the ability of this E. coli strain to survive and mulitply in the gastrointestinal tract."

Conculsions

It is important to keep in mind, while reading the above quotes, that the Wedum report (commissioned by the NIH) states that the microorganisms in question cannot be contained with any type of physical containment. Keep in mind also, that as you read this statement thousands of unknown genes from hundreds of different organisms sre being genetically transplanted into E. coli . And this is the very same E. coli K-12 which will sooner or later be ingested or carried out of the containment facilities to be spread over the biosphere. No matter how remote the danger--there must be some real question of an actual danger. If this was not so there would never have been an Asilomar conference, a moratorium on research, millions of dollars unsuccessfully spent on attempting to construct safe bacterial strains, guidelines for this research, guideline committees, and hundreds of hours spent studying this very question.

There has never been a potential for a global disaster of this order of magnitude. There is no predicting where the gene implant will end up and what its eventual expression will be. The one certain fact is that it cannot be contained. This work has been espoused to have many potential benefits for mankind. Will the cure be worse than the disease?

of human cancer. These same chemicals that cause cancer are powerful mutagens and are thought to be increasing the load of genetic diseases as well. This approach would clearly be very expensive to industry, requiring elimination of industrially important chemicals, greater safety precautions and more extensive pollution controls. It would also not result in major financial return to biomedical industries and the medical profession. Since resources for research are limited, proceeding along the gene implantation road detracts from more productive avenues. Thus, viewing our increased understanding of these disease processes as a benefit of gene transplantation is spurious and only serves to focus attention on the afflicted individual rather than on the societal causes of the diseases. Furthermore, we already have the capacity to treat the ills which cause the greatest amount of pain to mankind (e.g. malaria, intestinal parasites, malnutrition), but we do not use this capacity. We are unwilling to commit the necessary resources to those areas of treatment and prevention.
Why then do we wish to concentrate on these relatively exotic areas of medicine? Perhaps it is because it is here that there is a great deal of profit to be made by the medical establishment. The abovementioned common diseases are easy and inexpensive to treat, but the diseases for which gene transplantation offers either a tool for understanding or a method of treatment will be very expensive and consequently profitable to treat. The benefit in this case would seem not to be realized by the great majority of the sick, but by the industry which cures.

Conclusions

The above discussion points out much discrepancy between what is promised and what is likely to be delivered. We thus return to the question of who is at risk and who reaps the benefits. The benefits are there for the scientific community and for the biomedical establishment. But the rewards to mankind have proven to be much harder to find. If the public were fully aware of this situation would they be willing to take the risks that are being requested of them? They would probably be unwilling to accept even a much lower level of risk. And so, the hope of proceeding quickly with gene transplantation research seems to depend either on the public being kept out of the decision making process or being misled by the scientific community about the risks and benefits involved.

PHYSICAL CONTAINMENT

Physical containment is necessary, but deceptive. Four levels of physical containment have been proposed, P1 through P4, in increasing levels of containment.

P1 and P2 Levels of Containment

P1 and P2 basically represent standard microbiological practices. It is well known that biologists have a terrible safety record. Under P1 and P2 containment doors are unlocked, entry to the laboratory is wide open, and laboratories are not located in regions of limited access. No negative pressure system or air-filtration system exists. The major difference between P1 and P2 is that under the latter conditions a small sign, stating "Biohazards" is put in the area of the experiment, and then removed at its completion. Philip Handler, President of the National Academy of Sciences, best described this situation: "I don't think P1 and P2 contain anything." It is our feeling that P1 and P2 categories were set up to make P3 and P4 appear more stringent.

Analysis of Some Considerations Concerning the Gene Transplantation Technology

prepared by the Genetics and Social Policy Group
Boston Area Science for the People

June 8, 1976

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it be possible to maintain a low level of risk in large scale industrial operations? Who will write and enforce the guidelines? The National Institutes of Health guidelines apply only to academic research, yet private industry stands to profit greatly.

We must also face the possibility that some of the defense budget's 64 million dollars for chemical and biological warfare research might be used for the development of novel killing agents using genetic manipulation techniques.

BIOHAZARD REVIEW COMMITTEE AND LOCAL SAFETY COMMITTEES

Decisions about research projects which are to be pursued and the safety measures to be taken by researchers should be matters of public policy. These decisions should be overseen by a biohazard review committee. This committee could follow the efforts of the National Science Foundation to involve the public in these kinds of issues. The provisions of the National Science Foundation Authorization Act of 1976 directs the foundation to involve citizens' groups and scientists in the resolution of public policies and scientific matters.

The Genetics and Social Policy Group of SftP feels that the following points should be included in this biohazard review system:

(1) Biohazard decisions should be a matter of public record, including the arguments for and against the decision.

(2) Grant applications should include a Biohazard Impact Statement. This would describe not only local hazards to laboratory personnel but also possible danger to the general public including possible long term effects. This statement would serve as a means of self-education for the investigator, and should be readily accessible to people in the laboratory to encourage discussion of safety issues.

(3) The biohazard safety committees should also include substantial membership from populations at risk who are not the practitioners.

(4) Reports on biohazards should be included in the programs of scientific meetings. Courses in the general area of the social and biological impact of biomedical research should be rapidly incorporated into educational curricula.

(5) Local safety committees, like the new Biology Workers Health and Safety Committee at MIT in which the Genetics and Social Policy Group of SftP has been a participant, should be organized and should include laboratory technicians, custodial people, and clerical workers. The formation of such committees is mandated by the National Institutes of Health guidelines themselves.

Unless the workers organize themselves, these committees will probably be composed entirely of research directors, who under the competitive pressures of scientific research, will tend to ignore matters of safety. It is up to each and every one of us to insure that our rights are observed.

It would also seem important to establish procedures that will assure continued epidemiological monitoring of people (and their families) in places where DNA recombination experiments are peformed. The National Institute of Occupation Safety and Health (NIOSH), which under the Occupational Safety and Health Act (OSHA) of 1970 was charged to determine the potential dangers of hazardous chemicals in the workplace appears to be the appropriate agency for this task.

CONCLUSIONS

Scientists have written much about academic freedom which allows them to pursue scientific interests wherever they may lead. However they forget that their research is mostly financed by public tax money, spent to improve public welfare, not to indulge the whims of scientists. As population geneticist Richard Lewontin says, "Scientific research by its very nature has outside implications and consequently there is no inherent right to do anything a scientist damn well pleases."

Senator Kennedy of Massachusetts is convening a public hearing of the Senate health subcommittee on genetic research and bioethics which will hopefully discuss and propose legislation aimed at precisely the questions this pamphlet raises. We hope the American taxpayer gets a fair hearing at this conference, and that in the future all such public welfare decisions cease to be closed to only ranking professionals in their exclusive fields.

The Genetics and Social Policy Group of SftP notes the irony of the current situation. In the name of improving human health, newer and more potent threats to human health are being developed. It is unclear that these genetic technologies have been developed in response to national needs or whether they are simply the interests of professional scientists who make their livings with such developments.

—written by a committee from the Genetics and Social Policy Group of Science for the People.

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The Recombinant DNA Molecule Program Advisory Committee which was drawn up consisted of fifteen biomedical research directors, most of whom were directly involved with research on these new recombinant DNA molecules. They were asked to draw up regulations governing research. In July of 1975 this committee issued its report. The report essentially ignored all the warnings which had previously been issued, even the relatively mild concern expressed at Asilomar. The Genetics and Social Policy Group of SftP[4] and a group of geneticists meeting at Cold Spring Harbor, New York,[1] severely criticized this report, both for the content of the report as well as the composition of the committee. As a result of this criticism the committee withdrew its report and began writing a second one. However the composition of the committee was not altered. We and others insisted at that time that this committee was primarily serving the interests of those scientists directly involved in recombinant DNA work; they were clearly looking for the most watered-down guidelines. Nevertheless on December 4 and 5, 1975, at a meeting in La Jolla, California, this committee issued another similar report which will in all likelihood be the working guidelines.

The moratorium on active research, the considerations of risk involved, and the establishment of guidelines for such research which others have dubbed unprecedented, we consider to be publicly misleading. Such actions appear to have been taken to ensure the welfare of the general public, yet the public was neither informed, consulted, nor educated. The research directors have a vested interest and involvement in their own experiments. Can they be expected to act responsibly by taking full responsibility? If these experiments were to be put on trial, why then were experimenters allowed to act as prosecutor, judge, and jury? Commenting on the role of scientists and their self-regulation Senator Edward Kennedy stated, "It was inadequate because scientists alone decided to impose a moratorium, and scientists alone decided to lift it. Yet the factors under consideration extend far beyond their technical competence."

In their zeal to answer fascinating scientific questions, the research directors failed to open debate. Experts in such related fields as epidemiology and public health, occupational health and safety, and microbial ecology, who might have contributed to discussions of dangers inherent in such experiments were not consulted. Neither were the laboratory workers who actually performed the experiments allowed to participate despite the fact that they are exposed to the greatest risks. The general public, neither informed nor consulted, is also exposed to the risks involved in recombinant DNA experiments and should not have been allowed to abnegate responsibility. And it is precisely because such experiments are being conducted in the public interest with public money that the public should be educated about the pros and not deluded about the cons. Technologies such as diethylstilbestrol, asbestos, thalidomide, vinyl chloride, and dieldrin, which appeared completely beneficial at the time of their introduction have become intentionally or accidentally destructive of human life and the environment. Molecular biologists are in a position to benefit from the lessons of our technological present and not contribute to the inventory of tragic results of the past.

E. COLI: FROM TEST TUBE TO INTESTINE

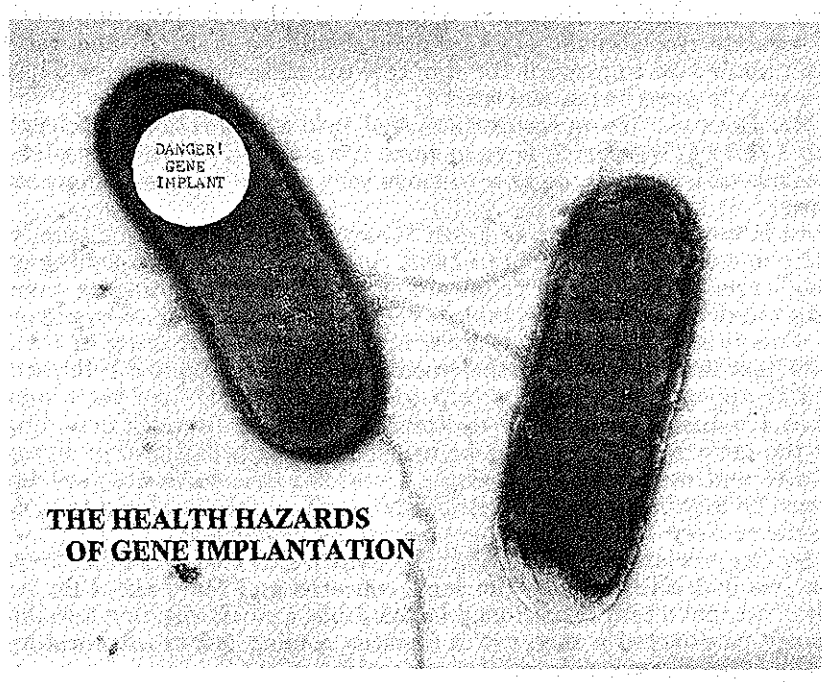
One of the primary areas of concern is that the bacterium *E. coli* is being used as the recipient for the recombinant DNA molecules. In as much as *E. coli* is a normal resident of the human intestine, pharynx, and is also a human pathogen, its choice as a recipient organism for gene implantation from foreign species seems reckless. Some strains of *E. coli* are pathogens and are the primary cause of diarrhea and other enteric diseases in humans. These strains can be responsible for death via secondary septicemias in otherwise diseased patients. With its universal, intimate relationship with humans, *E. coli* presents a fundamental ecological unsuitability for recombinant DNA experiments.

If the potential for such a serious problem exists, why is the current research being done with *E. coli*? Simply because the technology for employing *E. coli* has been developed and experimenters are unwilling to accept any further delays. If other bacteria were to be used it might require several years to sufficiently develop an equivalent genetic system which could act as recipient for gene implantation.

The practitioners have attempted to deal with these problems by developing physical containment systems and by constructing bacteria that cannot live outside the test tube (biological containment). The practitioners maintain that: (1) the containment apparatus will not allow the escape of the implanted bacteria into the environment, (2) even if some escape, they have been so extensively crippled that they are unable to persist outside the laboratory, and (3) these bacteria are unable to exchange genes with other bacteria, as normally occurs, so that the implanted genes cannot be transferred to healthy bacteria. These ideas are not supported by research into the physiology and ecology of bacteria and their plasmids. We[4], and other qualified scientists[5], feel the dangers are sufficient to warrant extensive tests to ensure that unwanted, foreign genes don't end up in the bowels of unsuspecting passers-by.

CRITIQUE OF THE SAFETY PRECAUTIONS AND THE PROPOSED GUIDELINES

Because some experiments are felt to be inherently more dangerous than others, different levels of physical and biological containment will apply to different experiments. It has been assumed that the physical containment facilities will be adequate although there has been no mention made of thoroughly testing them before the more dangerous experiments are attempted. In fact the number of reported infections in laboratories with special containment facilities of the most stringent type have been around 1650 in the last 30 years. There have been 423 cases of infection and 3 deaths in 25 years



THE HEALTH HAZARDS OF GENE IMPLANTATION

A PAMPHLET WRITTEN BY THE GENETICS AND SOCIAL POLICY GROUP OF SCIENCE FOR THE PEOPLE DISCUSSING THE HEALTH HAZARDS OF DNA-RECOMBINANT WORK.

Recent breakthroughs in the field of molecular genetics have improved greatly our understanding of how genes carry information from one generation to the next and of the role they play in specifying biological development and function. Associated with this new knowledge are powerful new technologies which allow the linking of genes from one organism to the next. Molecular geneticists have utilized newly characterized bacterial enzymes to couple genes from various living organisms to the common intestinal bacterium, *E. coli*. Theoretically any organism could act as recipient for such gene implantation. *E. coli* are now being employed because they permit easy, critical measurement of the technique's success. However, gene implantation technology also constitutes potential health hazards to both people working in the laboratories as well as the general population. For example one area of concern is that cancer causing virus genes might be implanted into *E. coli* or other recipients. These hosts might escape the laboratory and infect the public.

For these and other reasons the scientists involved in these experiments decided to institute a moratorium on all such research in 1974, a commendable action. But the practitioners of gene implantation have recently been criticized from both within the scientific community[1] as well as the general public[2]. Questions have been raised not only concerning how these experiments should be conducted, but also what they hope to achieve. Some scientists even question whether the experiments should be done at all.

For myself, I can give you three reasons how come I came, for example, into opposition.

One, I had been involved in a case where there was a genetic research on humans, male infants, for an extra Y chromosome, and I had the experience of talking to many medical people. When asking them, "Why do you want to tell the parents of this kid that he has a chromosome abnormality, when we don't know that it's going to do any harm, and even if it does, what can you do about it at the chromosomal level?" and these people said back to me, "Well pretty soon we're going to have the genetic engineering capacity to take out this kid's extra Y chromosome." So, one, from being out in the hustings, one has learned that, gee, the stuff wasn't so theoretical.

Second, I myself was not originally trained as a laboratory microbiologist. I was a field biologist. I had done microbiology out in nature, and from my professional background I have some sense of the extraordinary distance between the limited reality of the bench, where if you can't control it you don't study it, and you only study those things you can understand, and the realities in nature, where there's a million different organisms which are interacting in supercomplicated ways. That's one thing.

The third thing is understanding—from membership or our own biology worker's health and safety committee—the tremendous distance between a professor's view of conditions in a laboratory and a glassware washer's view.

I have often been in public debates where scientists are horrified that I would suggest some form of regulation of their activity. They feel they should be able to pursue whatever they want, and yet their glassware washers can't say, "Hey, I don't want to wash this glass. I don't want to do this. I want to work on something else now." So there's a big difference.

When you talk about regulation, you have, for example, in the Environmental Protection Agency people who are also microbiologists whose conception of the world of microbiology is different from the laboratory biologists. They just have a different viewpoint.

It's natural for them to worry about bacteria in the environment because they've seen that as part of their education and training. So the EPA scientists, when they came into this thing—I recently read their finding on this—they thought that the NIH had not proceeded responsably because their scientific background is a little different.

I heard Dr. Finklea at the National Institute of Occupational Safety and Health testify on this question, and his testimony, coming from actual concrete experience in trying to regulate safety in laboratories, was very different from the NIH, and he had a list of about 15 problems which he felt were totally unattended to because his concrete experience had come out of safety problems.

So I think the way you get organic regulation is to develop those areas of scientific apparatus whose formal concern is with the environment, whose formal concern is with public health, whose formal concern is with whoever's health, but also to find a situation where NIH doesn't see EPA as the enemy, and that I don't know how to do. I mean people like myself, sooner or later we have to quiet down. Our funding comes from the agencies that we're criticizing, and you're not going to survive. You have to pay the rent, like anybody else. It's

Mr. WHEELER. That's why I'm concerned about the whole private arena in terms of what do they do and what controls do they operate under.

Mr. THORNTON. That is the reason you suggested extension of the NIH guidelines to the private section, as modified in accordance with the input from the public, is that correct?

Mr. WHEELER. Yes; as an interim step. You may need more, depending on the problems that they have. But as a minimum.

Mr. THORNTON. Dr. Krimsky, did you have any comments with regard to this area?

Dr. KRIMSKY. I would like to reaffirm the issue that was intimated by several of the panelists.

I think, as a citizen, I am very eager to see that all this research, at whatever level and no matter who is doing it, be disclosed, exactly what is being done, what is being transplanted, because we face situations now where extraordinary properties can be introduced into microorganisms that may be exceedingly dangerous. Do we want, for example, to create new biological pesticides that if escaped might create tremendous hazards to our ecosystems?

We have to make sure that whatever research is done, whether in the private sector or the public sector, it is made known to the public so it could be scrutinized carefully.

Mr. THORNTON. Thank you.

Mr. Dornan.

Mr. DORNAN. Mayor, I notice in your biography that you have done some microbiological work or immunology work on syphilis.

I recall in 1968 that various counties around the United States would have their county health officers declare an epidemic; 1968 was the first time I heard this frightening word used in reference to syphilis, and then gonorrhea, and the word was used again in 1969 and 1970, while you were still doing research, 1971 and 1972, and then I lost track of it.

I just wondered, with all of the advanced, sophisticated concepts we're discussing here, if this country still has an epidemic of syphilis and if it has been around at epidemic levels for so long that the society in general is sort of anesthetized to the horror of the word "epidemic."

Mr. WHEELER. The whole question of syphilis is one which I think over the last 10 years there has been a leveling off in terms of the incidence, and so forth, of disease.

But indeed, gonorrhea is perhaps the most prevalent and the most common infectious disease in this country, and I'm not sure I would exclude the common cold from that list.

We are developing antibiotic resistant strains. There are ways of trying to play with that to get around it, but it is an epidemic in this country, and it affects young people, 9 and 10 years of age and the highest incidence probably in the 15 to 25 age group. But it is a problem, and it's one of those social problems that for a host of reasons people are unwilling or unable to discuss in a very sophisticated public manner.

Again, looking at other aspects of this, I think the Federal Government has been remiss in recognizing the seriousness of these problems and the breadth of the problems in the country because—and I am not pitching for research money, because I quit doing research—there

inhabiting bacteria instead of gasoline, or a similar contamination of fuel might occur in an airplane in flight.

Mrs. TAFT. It's just an example which I wanted to bring out about where we should put our priorities, and to me right now it's important that we make sure that priorities are placed where the money can be assigned to checking the fact that at least these NIH guidelines can be enforced. It's very difficult when you're working in a laboratory, and you might have someone coming in and checking up to see what you're doing. It's not the normal procedure of the way laboratories work or the way people who are accustomed to working in institutions operate. I think later on this week you will hear people who have serious concerns about that, from Princeton, too.

But I believe it's very important that we find ways that can be effective without necessarily hampering the work.

Mr. THORNTON. I certainly agree with that, and I think your comment is a very valuable contribution. There is a need to assess priorities in research and not go off in directions which are nonproductive or overly hazardous. I thank you for that comment.

Mayor Wheeler, did you have a comment?

Mr. WHEELER. Yes, Mr. Chairman.

I didn't indicate to you that I happen to be by training a microbiologist.

Mr. THORNTON. You're a professor of microbiology?

Mr. WHEELER. Yes, sir, and I sit in the very peculiar position that I happen to work in a department where the center of activity and advocacy for the recombinant DNA occurs in the university.

I have not discussed this communication with my department, Mr. Chairman. I will give it to him when I go back, because that's the way I think I have to operate.

I have just one question. I am concerned with how fast we go, what we do, and how it's done. But I have a question that if the knowledge now exists that somebody, either under regulation or clandestinely, is going to be doing this research. If the knowledge were not there and if 15 or 20 years ago a decision had been made that we would not permit—however we made such a decision—such research to occur, it might have been an appropriate time to have stopped it and said, "Let's put a moratorium on it." But it's here. It's not only here in our laboratories and our universities, but it's here in foreign universities and foreign laboratories, and at this point there is some voluntary communication and discussion of guidelines. But I hope the research is going to go on.

Now, in the committee that the university created to make the original decision, a compromise was impossible with one member of that committee, because that member felt that this research should not proceed under any circumstances. The other nine members reached a compromise in terms that it should go on, but under very defined and controlled conditions and facilities, and so forth.

So I guess the whole question of compromise depends upon whether the compromise is that we're not going to do it at all—and some people will not compromise that issue—or that it will be done and done under certain specified conditions.

The other question—and I want to strongly support what Dr. King has said in terms of national policy—yes, we have policy, but unless

Now, I do not believe that the American public knows that their NIH Committee for funding research on how tobacco causes cancer is operating that way.

Furthermore, I believe that the American people that are able to read an article which says,

> This component, tetrahydrate, domiciled in cigarette smoke causes cancer because it damages the villae cells of your ducts and it keeps them from sweeping up the particles back out of your lungs.

If they had discrete knowledge I think they would be much better armed and able to make a choice.

As a matter of fact, there is a woeful—I won't say suppression—but a woeful underdevelopment of information of biomedical research on exactly how tobacco causes cancer, and I think as a result of that the American people have not been able to make an intelligent choice of risks versus benefits because the policy on research on how tobacco causes cancer has been under the control of the wrong people, and not, for the benefits and hazards to be under congressional scrutiny.

Mr. THORNTON. I should think that if you were to advocate a risk-free society we would have to ban tobacco smoking, ban saccharin, and right on down the list.

Dr. KING. I'd like to back off on that, because I didn't advocate a risk-free society. Organisms are not like oil spills. They grow and reproduce themselves. You can't wipe them up once they get out. That means the issue of genetic engineering is qualitatively different from all of the pollution issues. If you make a mistake and an organism like E. coli gets out, you cannot clean up E. coli from the environment, so that accident is irreversible.

Mr. THORNTON. Assuming that the E. coli is not limited itself or biodegradable.

Dr. KING. Right. Suppose there's been an error in assessment. Let's say the biodegradable ones are biodegradable, and we'll talk about those experiments done in the ordinary strain, which has been around for millions of years, and we make no assessment of that and we know it can survive because that's where we got it from.

Now, if we slow up research and, let's say, God forbid, we close down the laboratory at Princeton University from doing just this technology, not from doing scientific research, not from asking any questions they want to ask, just from one route to the answer, will the pipettes go away? Will the scientists drop dead? Will the journals disappear from the library? Will scientific progress stop? Absolutely not.

We aren't talking about freedom of inquiry. We're talking about irreversibly altering the environment, the manufacturing of new organisms.

I can ask questions I want to about blood clotting, but the moment I want to cut off your ear to see if there's sufficient blood clotting factors to stop the flow, it's a different question.

Mr. THORNTON. That's where you get to the National Commission for the Protection of Human Subjects.

Dr. KING. Right.

Let me conclude with an example from another area.

Scientists tend to cry bloody murder if you suggest that there's any such thing as an incorrect priority in basic research, and yet these same scientists would never dream of saying to one of their graduate students, "Just do any experiment that comes to your mind in the lab. Any experiment is as good as any other experiment." They're not. They set priorities, at any level they set priorities, and then assess them. We should set priorities on biomedical research policy because if we don't we're going to find ourselves in a situation where the scientific community, rather than solving the problems of ill health that we have, are just generating a whole new spectrum of new health hazards because there's no coupling between the research policy and providing health to the American people. It's like chemical companies who, in the name of progress, synthesize a whole variety of new chemicals, none of which we need, and most of which we are eventually going to get poisoned from, and dump them out into the rivers and onto the ground and say, "This is progress."

The same thing will happen to the scientists, unless we get connected to the public so that we don't end up on opposite sides of the fence, and that's going to involve legislation which says that research is part of health policy; we need prevention; we need to preserve health in this country; and not just push back the frontiers of understanding.

Thank you very much. I'm sorry for going on too long.

Mr. THORNTON. Thank you very much, Dr. King, for your testimony.

I would like to open the questioning with a general inquiry as to whether it is correct to say that we do not now have a national research policy.

It seems to me that an argument can be made that we have a policy, a national health policy, which seeks to minimize risk and to provide certain guidelines for the acceptability of risks. This policy deals more with the production and dissemination of biological materials which are produced commercially or institutionally. But the national research policy is to promote scientific research, within certain limits, such as those recommended by the National Commission for the Protection of Human Subjects, and it is appropriate, I think, to set such limits on research.

Dr. KING. It seems to me that that's like saying, "Our foreign policy position is to promote foreign policy."

We have the problem that there's only limited national resources; there's only a limited pool of money that we spend on research. Choices are always being made. If you put a lot of money into genetic engineering, that doesn't help you identify carcinogens in the environment. That's the choice that you make to develop knowledge in one area, and that means the underdevelopment of knowledge in another area.

I remember a couple of years ago I was very upset about spending by the National Cancer Institute, and I wanted to write to my Representative, about his vote on this issue, and then I discovered that there hadn't been any vote on that issue. So I went to the library and I found that there was a policy, and it was articulated in the report, the Chemicals and Health Report of the President's Science Advisory Committee. As far as I could tell, this had never been discussed on the floor of Congress.

a little bit of an explosion is not a tolerable compromise, and we have the same situation here where you're talking about the release of genetically altered organisms in the environment.

Now, many people have talked about the problem of educating the public. Those Cambridge City Council hearings educated the public like nothing else in the scientific community has ever done before.

Now, why was that? It's because of something on which participatory democracy is based, which is that if people can have a say in something they will find out about it. You cannot ask people to learn about the details of genetic engineering if they know there is nothing they can do about it, that some decision is being made in a closed committee in La Jolla, California or in Woods Hole, Mass. But if they know that their city council, in which they can have a voice, is taking up the issue, they will find out about it, and the 400 or 500 people who sat silently intense, taking notes at those city council meetings, they were going to educate themselves about genetic engineering because for the first time there was something they could do about it.

I do not believe that it is possible to have a democracy without an informed electorate, and I do not believe you can ask the electorate, to inform themselves about something and then give them no power to speak about it.

Local action on these things is the best way to develop a real participatory democracy.

I think we desperately need a national commission to look into this. But why shouldn't we also have a Massachusetts Commission? Who's to say that the Massachusetts Commission wouldn't come up with some better ideas and a better set of guidelines than a national commission? When you have a pleuralistic society, why go through monolithic modes, really unnecessarily?

So I would like to second Dr. Krimsky's point about the multiple inputs.

I would like to come to what I originally brought up.

I think that local preemption on this issue is an absolute necessity because that's where the knowledge is. It's locally that people know whether or not students walk in or out of the lab; they know whether there's a union representing the laboratory workers; it's locally that they know whether the conditions are safe; it's locally that they know whether the custodians working the night shift are always going into the lab when nobody else is going into the lab. Those things are critical in understanding the health monitoring process.

Let me close with the question of biomedical research policy in general.

Most of the ill health in the American population has its origin in local conditions, whether it's exposure of the factory worker to toxic solvents, the paint workers to heavy metals, little children to lead poisoning, tenement dwellers to infectious disease due to overcrowded living conditions, or the unemployed to malnutrition, or hospital patients to infections that are acquired in the hospital.

Now, Harvard and MIT are great universities, but there is no connection between biomedical scientists in these universities and the people in the surrounding communities who are sick and ill, even though we are all supported by the National Institute of Health, paid for by the taxpayers, including those in Cambridge. We have never

committee. They made a number of sharp criticisms of the guidelines, all of which were in substance rejected by the committee, who quite fiercely resisted tightening the guidelines.

I would like to note that at this time the construction of genetically altered strains of organisms was about to proceed, and yet there had been no substantive congressional proceedings at all. That is, there was no way by which a concerned citizen or scientists could have any meaningful input. National policy had been made that we would go ahead with genetic engineering as a tool of biomedical research, without ever having any review of discussion by the elected representatives of the people, and let me tell you, some people were really actively frustrated. Something was going on that we were scared about, and there wasn't a damn thing we could do. Some people, like myself, who are in a very privileged position, could attempt to speak out because we have the credentials, but even so, it was difficult.

Mr. THORNTON. We're attempting to provide that avenue of communication.

Dr. KING. Right, and I'm very appreciative of it.

Given this background of the lack of democratic process, the Cambridge City Council call for public hearings was a critically important event, not just for the people of Cambridge, but for the whole country. This was the first time the taxpayers, who support the research, in whose name it is done, and who bear the substantial risks, were able to speak.

Now if I may make a comment on protecting public health?

If there are accidents with new organisms, the accidents occur locally. They occur in some physical laboratory where a graduate student may be splashing when he shouldn't splash, and there is an aerosol and it gets in his nostrils, and he walks out of the laboratory and he sneezes, et cetera, or a professor who's trying to get some results quickly because he has a paper that he wants to publish moves a little too fast and sidesteps ordinary procedures and breaks a flask, *et cetera.* Those are the way the accidents are going to happen. That is, the people who work there are going to be the carriers of any infectious agents. That means that when we protect them it's altruism. We protect them to protect us. If we can't keep people in the laboratories from picking up these organisms we can't prevent transmission to ourselves. So therefore it's very important that the safety procedures be tight locally because that's where the accidents happen.

Now, you might ask what could the elected officials of Cambridge accomplish that the National Institute of Health Recombinant DNA Molecule Advisory Committee could not?

They could accomplish a great deal, and they did:

1. They invited testimony from the opponents of the research, since they were primarily concerned about hazards. It was in their interests to bring out, rather than suppress, this testimony. That's very important to bear in mind.

2. They took testimony from laboratory technicians as to the actual conditions in research laboratories. Now, to my knowledge, neither the NIH Committees nor the Congress have yet taken testimony from these people, the actual people who work there, who carry on the labor.

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STATEMENT OF JONATHAN KING, DEPARTMENT OF BIOLOGY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Dr. KING. Thank you.

First, I'm very pleased to be here.

I would like to apologize to the committee for not having a prepared statement. I prepared one and then I learned of changes in the pending legislation and I scrapped it and wrote new testimony.

Mr. THORNTON. You have permission to amend and modify your testimony at any point up until the time that you say it, and then if you have clarifications later on we will be pleased to accept them.

Dr. KING. Thank you.

My name is Jonathan King. I reside at 136 Williams Street, Boston, Mass. I am employed as an associate professor of biology at MIT, where I do research and teaching in molecular biology. My professional training includes a bachelor of science in zoology from Yale University, a Ph. D. in genetics from Caltech, and postdoctoral training at the British Medical Research Council. My area of research is in the genetic control of virus structure. I also teach a course in social issues in biology, and have been actively involved in a number of issues concerning genetic research on humans, and I was a member of the Genetics Group of Science for the People, which was a citizen's advocacy group that operated in Cambridge around this issue.

I might say that Time magazine recently referred to the Science for the People as a radical group. Science for the People is radical the way the Sierra Club is radical to people who want to cut down the redwoods. It's just a group of people involved in science and technology who have been concerned about the misuse of science, and it's about as radical as the Sierra Club is.

I'm very pleased to be invited here to testify concerning the role of local communities in science policy. There is some irony in a professional researcher testifying on local involvement, rather than on the scientific aspects of the genetic engineering controversy. This reflects the fact that people like myself, who believe that gene transplantation is extremely dangerous, and who have proper scientific credentials,

relationships, the relationships between various units that may be engaging in the research and local government. That's, again, the Federal, State or private industry activities and local government.

The final point that I wish to stress in terms of what we may need, is comprehensible data in this area which local officials can understand and utilize for their own education and for public education regarding the major issues related to recombinant DNA research. We also need solid information concerning the public health and environmental issues related to that research. Such comprehensible information is essential for the education of the elected public officials and for the general public because there are people with all sorts of limited knowledge and fears, and which may be real or unreal in terms of the terrible things that can happen from accident or even from conscious manipulation in this arena.

I think I'll close this by saying that ultimately, as the public becomes more aware of potential risks and misuses inherent in this research, it will be necessary to have candid and believable answers for the more sensitive questions of undesirable potentials of genetic engineering.

Thank you.

Mr. THORNTON. Thank you very much, Mr. Wheeler, for a very thoroughly prepared statement and a very fine summarization. We do appreciate your oral outline of the high points of your prepared statement.

Of course, you have focused upon one of the very real dilemmas which must be addressed by policymakers, and that is how do you go about establishing standards, which, if we have been told correctly, must be national in scope and perhaps adopted worldwide.

Also, how do you reconcile the national need with the need to have communication and input from the local communities, which are, as you point out, most directly involved, or most immediately involved, perhaps I should say, in the activities.

We will be looking for some proposed answers to that question as we go further.

Mr. Hollenbeck, we've been following the suggested procedure by requesting each of the panelists to make their presentation and then asking questions, but if either you or Mr. Dornan have any questions of clarification which you would like to ask at this time we'll take them before we proceed with our last witness.

Mr. HOLLENBECK. No. I'll wait.

Mr. THORNTON. Mr. Dornan.

Mr. DORNAN. No. Thank you, Mr. Chairman.

Mr. THORNTON. Fine.

Our next witness, Dr. Jonathan King, of the Department of Biology, Massachusetts Institute of Technology, is a very notable authority in this field. I had the privilege of hearing Dr. King participate in a debate sponsored by the National Academy of Sciences. I'm not sure that it was a debate. It was au experience. I did enjoy listining to the proceedings of that forum.

You're welcome to our committee. We'd like to ask you now to present your prepared statement and then we'll open the panel to questions.

[Biographical sketch of Jonathan King follows:]

work will proceed under existing NIH guidelines; and that high level risks, such as P–4, and so forth, will not be permitted, at this time, in our community. I trust that such an ordinance can be adopted.

The university community. I've given you in my prepared report a brief reference to the University of Michigan approach to this type of research. I also suggested that perhaps one should address the University of Michigan for detailed reports on the process that has occurred there. Indeed, during the course of a year or so, through a number of university committees, and, most importantly perhaps, the first one, which was composed of about 11 people, all university affiliated, but only about 4 of that 11 could, by any stretch of the imagination, be called bioscientists in the usual interpretation. The question was: Shall this research proceed on the campus of the university? And the ultimate decision, I think after 6 months, was that it should, but that it should under certain defined and constrained conditions. Then from there, the university proceeded to follow up those recommendations.

The only one followup that I would mention at the moment is that there ultimately was appointed a nine-member committee called the Biological Research Review Committee, composed of nine people, eight university and one nonuniversity affiliated person. That nonuniversity affiliate was recommended by the mayor in a list of three or four nominees.

I've spoken of some of the problems and some of the virtues of that process at the university, as I perceive them.

You've asked: What new mechanisms would be desirable and implementable?

I think that we have to look at the question of licensing, and I am not at this point of a fixed mind in terms of whether that should be a Federal license, or a State license, or a local license. I don't want there to be too many licenses, but I think there has to be a license, as I think we do in some of our other areas of interest in research activities. But I think perhaps a State license might be a useful one. I attempted to come up with some legislation that would control things in my local community. Then suddenly it occurs to me that a VA hospital is not in my community, and there are other activities going on in the townships around us that are potentially affected. So whatever we did as local government would not affect those outside the city limits, therefore, perhaps there ought to be a State regulation.

But I think it's also very important that the local government's prerogatives should not be usurped, either by the Federal Government or by the State, because it's our community in which the activities will be occurring, and it's our people who will probably have the greatest risk.

I think we have to reexamine whether or not the Federal Government can retain the power to say to the citizens of Ann Arbor that:

We're going to do this research at the Veterans' Hospital, or any other Federal facility there, and we really don't care what you think about it.

I think that relationship has to be examined and changed.

I want to make a correction on page 8, if I may. In C, part 1, I have on the third line "covert role." I meant "overt," obviously. The State, as far as I know, has not played any overt role.

Mayor WHEELER. Looking at the role of local governments, it might be important to know something about the background of the various communities where debate and discussion may be occurring, and so I've given some basic information about the city of Ann Arbor, and I will not go into any details on that.

There are a couple of things, however, that I would like to mention to you, which I think are significant in this question we are discussing.

There's the question of who will be conducting DNA research or any related activities. At the present time in our community, within the corporate city limits, we have two institutions that are prime targets for such research and activities. One is the University of Michigan, where research is now moving ahead, and the other is the Parke-Davis Pharmaceutical Research Laboratory. A third institution that I think has a very good likelihood of getting into this business sooner or later is the Veterans' Administration hospital, which is unique in the sense that it is a federally controlled institution. Furthermore, while it's within the corporate city limits, it's located on a township island within the city, an occurrence that may not be unusual in many communities, and maybe we ought to keep such factors in mind as we look at this whole issue.

I would just state that the University of Michigan is itself, by State constitution and statute, almost an autonomous agency. It is not required to discuss its plans and its programs and policies with the city of Ann Arbor. In some instances they do, and in some they don't. Some, it's obvious they must discuss, like streets, fire, sewer, water, and so forth. Others, are not necessarily discussed with us.

I point out on page 3 of my prepared statement that it's my understanding at the present time that there are no specific regulations and guidelines, however, they are being formulated, to cover the pertinent activities of private industry. To my knowledge, private industry in the interim is neither prohibited from engaging in this specific research nor legally mandated that such research be performed under existing NIH policies and guidelines.

I think this is an issue that must be addressed.

In terms of public participation, the general public has a right to know. I think they are endowed with this right, and they should know beforehand what the basic nature of the research activity is, and if it poses a potential threat to the health, safety and welfare of the community.

In matters of a scientific nature such as these, the nature of the activities and the potential risks, whether they're real or imagined, short-range and long-term risks occurring should be given; and there should be proposed regulations regarding the control of the risks. These things should be done, as often is not done, in language that is comprehensive and understandable to the average citizen.

Special attention should be given to informing and involving those communities or segments of the population who, for a variety of either factual or emotional reasons, may feel especially threatened by the activities under consideration.

In the case of genetic engineering, it is not unreasonable to anticipate that in different nations of the world, including our own, certain groups may fear that in a future decision to achieve racial purity, for example, or maximum human productivity, however defined, or for

The following generalizations therefore appear reasonable to me:

1. *That these new discoveries will mandate a continuing review of policies and guidelines and appropriate revisions, at frequent intervals.*

2. *While it is necessary to have federal policies and guidelines that apply universally to certain aspects of DNA activities, there will be the conduct of these activities under varied state and local conditions. It is my judgment that such variations of policies and regulations, under the broader federal umbrella, could be very valuable in the refinements that will be needed in federal policies and guidelines.*

D. *How Can Congress Use Local Information More Effectively In Evaluating Federal Science Policies*

1. *The first obvious answer is that the Congress should establish a list of minimum information that it would desire, with provisions for additional information.*

2. *The Congress should suggest several mechanisms through which local governments, agencies and organizations could report their information.*

   For example, the Conferences of Governors and of Mayors and the National League of Cities (Counties and Townships) could be requested to establish procedures with their respective units to serve a liaison function.

3. *A mechanism should be established through which organizations with special interests (ethical, religious, legal, racial, sex, et cetera) could communicate their concerns and recommendations.*

4. *Finally, a federal body (possibly NIH) or a broadly represented body of citizens responsible to the Congress or an appropriate federal agency could analyze and evaluate the varied local information and prepare recommendations for the Congress or its designated Committees.*

E. *What Significant Local Issues Are Now Inadequately Addressed At The National Level*

1. *The most obvious one to me is the absence of official policies and guidelines for research and/or development activities by persons or institutions not covered now by existing NIH guidelines.*

2. *Mechanisms for defining and dealing with questions of responsibilities and jurisdiction that may arise between local governments and federal or state agencies operating with such communities. One important issue of this nature concerns fiscal responsibility for community harm that may result from DNA research and development.*

e. *a demonstration that open and candid debate between individuals (or groups) with strongly differing opinions on important fundamental issues can be conducted in a manner that can reach a workable compromise, where a compromise is possible.*

Some of the problems that I see in the process as carried out, are as follows:

a. *that City government was not invited (nor did it request) to become involved officially with the Board of Regents as a decision-making partner. I believe that the value of such a partnership is that the approximately seventy thousand local residents, not directly affiliated with the University, have important rights, considerations, and obligations that should be protected in an atmosphere of cooperation.*

b. *there is no minority representation on the Review Committee, either from within or outside the University, and except for the female representative of the laboratory technician group, there is no other female Committee member.*

c. *the number of non-University-affiliated members of the Review Committee should be increased. An alternative would be to speed up the establishment of a general overview Committee, with an approximate even distribution of University/non-University affiliated members.*

B. *What New Mechanisms Would Be Desirable and Implementable*

1. *Because the DNA recombinant molecule research and development implications and risks extend beyond any local community boundaries, it appears that many activities and concerns must be on a national and/or statewide basis. Perhaps a state license should be required, but the application should be forwarded through local government. To minimize conflicting basic policies, regulations and guidelines within the State, perhaps a broadly representative State Commission should be established to deal with the issues raised in your communication.*

Some specific ideas that I am exploring to offer to our City Council are as follows:

a. *reactivation of the City Board of Health and charging it with the duty of recommending policies and procedures to deal with this issue, including recommendations to establish ad hoc committees to deal with special issues.*

b. *to request formation of a policy level committee including representatives of the City and those agencies engaged in or preparing to engage in such research.*

c. *to request our City Administrator to review policies and procedures of certain City departments and to recommend any changes or additions needed for community protection.*

d. *specifically, I was prepared to submit to our City Council two resolutions dealing with DNA recombinant molecule research, but did not for the following reasons:*

   1. *unable to get prior bi-partisan support for one resolution calling for an environmental impact statement.*

   2. *my own realization that a proposed ordinance to establish legal requirements on the conduct of non-University sponsored research within the City would be ineffective because some of the research could be done in contiguous areas outside the City's jurisdiction where our rules would be unenforceable.*

e. *it is my specific intention within the month of May 1977 to introduce an ordinance or resolution requiring any person or institution to notify the City of an intention to undertake DNA research, the type of any research that may be in progress and to require that, until new federal guidelines are promulgated, any such research must be conducted under existing NIH guidelines. Further, research at the P-4 level would be prohibited at this time.*

2. *<u>In The Unversity Community</u> - for the better part of a year, major issues regarding Recombinant DNA research were studied and discussed by regular and special ad hoc University committees under the immediate purview of the Vice President for Research. The resulting findings and recommendations were forwarded to the President of the University for his review and then for action by the elected governing body of the University, the Board of Regents.*

Additionally, for reasons given above, the Veterans Administration Hospital could undertake this particular research (and other) without direct, official contact with the City Council.

It is my understanding that specific regulations and guidelines are being formulated to cover the pertinent activities of private industry. But, to my knowledge, private industry, in the interim, is neither prohibited from engaging in this specific research nor legally mandated that such research be performed under existing NIH policies and guidelines.

With this background, I will comment on those issues which are raised in your letter regarding public participation and local actions in scientific and technical decision-making, using DNA recombinant molecule research as a case study.

I. Public Participation In Decision-making:

A. The General Public - the public at-large is endowed with the right to be informed beforehand of those activities under consideration in the community, which activities may pose a potential threat to the peace, safety, health or security of the individual and/or the community.

1. In matters of scientific endeavors, the essential nature of the activity and its potential, real or imagined, benefits and risks (enumerated on the basis of long and short range probabilities) and proposed regulations regarding risk controls should be prepared as concisely, as feasible and in language and style that make the critical issues understandable and comprehensible to the average citizen.

2. Special attention should be given to informing and involving those communities or segments of the population who, for a variety of factual and /or emotional reasons, may feel especially threatened by the activities under consideration.

In the case of genetic engineering, it is not unreasonable to anticipate that in different nations of the world, including our own, certain groups may fear that in a future decision to achieve racial purity or maximum human productivity (however defined) or for political reasons, their very existence or the nature of their existence may rest in the balance.

3. Because of the fundamental ethical, moral, legal and general social implications of many scientific undertakings, special attention should be given to insure that these concerns are appropriately represented from the general public.

4. The above informed members of the general public should have a meaningful voice in decision-making and also in the continuing monitoring and evaluation of the activity.

CITY OF ANN ARBOR MICHIGAN

100 North Fifth Avenue, P.O. Box 647, Ann Arbor, Michigan 48107

Phone (313) - 994-2766

May 3, 1977

Office of the Mayor

Honorable Ray Thornton, Chairman, and
Honorable Members of the House
Subcommittee on Science, Research and Technology

I am Albert H. Wheeler, Mayor of the City of Ann Arbor, Michigan. I wish to express my gratitude for the opportunity to appear before you to discuss various aspects and implications of local actions concerning DNA Recombinant molecule research. However, because of the overwhelming significance of this research to the future of mankind and because of my awareness of the frequently cited potential benefits and risks inherent in genetic engineering, it should be added that I am participating in this meeting with an unusually deep sense of ethical and social responsibility.

It should be noted that time constraints did not permit prior consultation with or review by the City Council or other City officials. Therefore, this is my personal statement as Mayor. I will share it with other City and University officials.

We all recognize the difficulty of an in-depth coverage of even a very limited aspect of this important subject in the allotted ten minutes. Therefore, at this time, I will concentrate more on the policy-implications of the actions rather than the actions themselves, which transpired in my community regarding the conduct of DNA recombinant molecule research at the University of Michigan. Perhaps in response to some of your questions and assuredly in additional written submissions to the Subcommittee, I will describe the process and procedures in more detail.

In the belief that your analysis and evaluation of actions in different local communities will be enhanced by some understanding of these localities, I will give a brief overview of a few important characteristics of Ann Arbor which have influenced and/or will influence local policies.

Ann Arbor is a community of about 105,000 people, of whom approximately 35,000 are University of Michigan students. The median family income is estimated between $17,500 and $19,500.

The University is not only the major employer in the City, but its faculty, staff, students and its obvious public mission contribute significantly in shaping community mores. One important community objective and characteristic which, in large measure, has its strongest initiative and support from within this University community is the maintenance, as far as is feasible, of a safe, clean environment. Consequently, there are no heavy manufacturing industries or factories within the City.

Mr. THORNTON. Your latter statement does relate to one of the issues to which our subcommittee is giving some attention, namely, the distinction which may or may not be drawn, and we're addressing the question of whether it should be drawn, between research and commercialization of the products of that research. This is a very interesting and fundamental question which must be addressed in any determination of these issues.

We do thank you for your statement.

I would like to mention very briefly one element of your statement, and ask if any other committee members have any clarifying questions before we proceed to the other panel members. I was struck by your suggestion that you take a position similar to that which is required at an intersection with a flashing yellow light: slow down and proceed with caution. I wonder if you would give us that same advice, those of us who are called upon to make a determination on this very fundamental and important issue. Is it appropriate for us also to gather as much information as possible, to slow down and proceed with caution, so that we do not through haste make error in our determination.

Mrs. TAFT. I think, from speaking to Dr. McCullough earlier, that you have already embarked on that procedure. So I believe you are on the right track; the fact that we are here today points to that.

Mr. THORNTON. I just thought that your analogy was appropriate perhaps not only for the scientific research but also for the determination of the basic societal issues with which we are dealing.

Mrs. TAFT. Yes, definitely.

Mr. THORNTON. Thank you very much, Mrs. Taft.

Mayor Wheeler, we are delighted to have you join our panel now.

We are proceeding on the basis of asking each of our panelists to make a statement, and then we will open it to questions addressed to all the panelists.

But before doing so, I would like to ask Mr. Dornan if he has any questions at this time.

Mr. DORNAN. Thank you, Mr. Chairman. Not at this time.

Mr. THORNTON. Thank you.

Mayor Wheeler, then I would like to recognize you at this time to proceed.

Mr. WHEELER. Thank you very much.

[Biographical sketch of Albert Wheeler follows:]

ALBERT H. WHEELER

Birth: December 11, 1915, St. Louis, Mo.
Home address: 234 Eighth Street; Ann Arbor, Mich.
Bnsiness address: Department of Microbiology, Medical Science Building No. 2, Michigan Medical School, Ann Arbor, Mich.
Mayor's office: City Hall, 100 North Fifth Avenue, Ann Arbor, Mich.

Education

A.B., Lincoln University, Pennsylvania 1936.
M.S., Iowa State College (Bacteriology) 1957.
M.S.P.H., University of Michigan (Public Health, 1938).
Dr.P.H., University of Michigan (Public Health and Microbiology) 1944.

Employment

1. (*a*) 1944 to present; University of Michigan Hospital and Medical School; (*b*) Currently: associate professor of microbiology, University of Michigan; (*c*) major current responsibility—teaching; and (*d*) 1944–1970: Principal research, serodiagnosis and immunology of syphilis.

Two small West Coast firms are already in the specilized field. Cetus Corp. of Berkeley has as its consultants professors at Stanford University, including Nobel Prize winner Joshua Lederburg. The other firm, Genentech, headed by Herbert Boyer of the University of California at San Francisco, is currently attempting to synthesize human insulin with gene-splicing techniques.

A leading opponent of recombinant DNA research, Liebe Cavalieri of the Sloan-Kettering Cancer Foundation, recently told the Princeton citizen's biohazards committee that such private firms as Cetus represent the greatest human threat because of the lack of controls over the research conducted, and the push for quick results.

Should Mr. Johnston be successful in putting together his project it would appear to be the third such private firm dealing exclusively in DNA recombinant research, and the first in the East.

He pointed out that there was no intention to locate in the Princton area. The most likely sites were near Washington or Boston.

Washington is an ideal site because the attitude toward the research is better. "Research is already going on there and there is some degree of tolerance," he said.

His plans are for a moderately hazardous P3 laboratory to be established in eight to nine months. The proximity of a P4 laboratory, conducting the most dangerous research, is another plus for the Washington area, he noted.

Ft. Detrick in Maryland, once used to develop biological warfare weapons, will be converted for the most hazardous types of DNA research by the National Institutes of Health. The facility may be accessible to private researchers who need to do part of their work at the P4 level, Mr. Johnston indicated.

Despite the fact that drug companies are setting up their own DNA laboratories, Mr. Johnston maintains that there is still a place for a small, private, specialty firm.

"Because of the political and emotional implications of such research, many firms will not set up their own labs for a period of time. Many do not want to take the flack of explaining their intentions to a local community.

"Imagine the difficulties if Princeton University itself is having a tough time. People would trust the university before a commercial company. Those companies instead will be willing to buy a product from XYZ little company which would be willing to take the flak."

He drew a parallel with the Dow Chemical Company's troubles when it manufactured napalm during the Vietnam War.

"They finally figured it was not worth devoting the time and effort to manufacturing it and it ended up under manufacture elsewhere," he noted. Dow campus recruiters found themselves the subject of protesters across the nation during the war because of the manufacture of napalm.

The controversy surrounding DNA research will probably prevent the new firm from going public.

"There are enough factors to contend with and regulations to comply with without having problems with stockholders," Mr. Johnston pointed out.

He said Cetus's annual report came in for considerable criticism at a recent meeting in Washington on DNA research sponsored by the National Academy of Sciences.

problems as who should do the inspection, who shall pay for it, and other issues that, again, can only be handled effectively by national policy.

I am of the opinion that much can be gained by some continued involvement on the local level, or "from the ground up," as Senator Kennedy has stated. In connection with the proposed bill H.R. 4759, I believe it is important that local communities retain some option of issuing ordinances that would include some members of the community on the institutional review committees required under section 471 of the bill. These public members could serve as a useful liaison between institutions involved in recombinant DNA research and both local and Federal Government. I do not believe that State regulation can be particularly effective; citizens' interest lies in the community; the need for uniform public policy requires Federal control.

Finally, I would like to urge this committee to consider refining somewhat the specifications for the people who would serve on the advisory committee to the Secretary of HEW as mentioned in section 479 of the proposed H.R. 4759. Of the eight members of the proposed committee that "shall not be engaged in or have financial interest in recombinant DNA research projects," I believe it is important that a significant number should be actively involved in some scientific endeavor so that recommendations made by those involved in this research itself shall not remain unchallenged by those who feel they must defer to the more knowledgeable.

In both the intellectual and practical sense, recombinant DNA technology spells access to enormous power. It has raised searching scientific and societal questions. Let us be prudent—let us use this power wisely.

I have one other small item that I would like to present before this subcommittee.

Mr. THORNTON. Please proceed, Mrs. Taft.

Mrs. TAFT. Thank you.

A few weeks ago, the April 8 issue of Science Magazine carried an advertisement which you may have seen, and if I may read it? It says:

> Entrepreneur: Wanted, the president for a new company creating products utilizing recombinant DNA techniques; prefer background in this technology and in business. Contract Robert Johnston at——.

And the phone number is given—for Johnston Associates, Petty Brook Road, Princeton, N.J.

This gentleman was contacted by one of the people on our committee, and we were told:

> Oh, don't worry, I don't plan to do any of this work in Princeton. It would be done either in Cambridge, Mass. or in Washington.

This week there was an article in our local newspaper about him and I'd like to read just a couple of paragraphs from it.

> Johnstou Associates, headed by Robert Johnston out of his Petty Brook Road home, is pursuing that delicate issue in the interest of making significant profits for investors.
>
> Mr. Johnston describes himself as a venture capitalist, a middleman attempting to combine those with risk capital to spend with others with the scientific skills and business savvy to run a private gene-splicing laboratory.
>
> "Our business is raising money for young, high technology companies. We have been mainly in the medical instruments business, but now we are moving into the microbiological field," Mr. Johnston explained this week.

much less with those of the profit-oriented regions of a competitive economy.

I therefore take a position similar to that which is required at an intersection with a flashing yellow light: slow down and proceed with caution. I can support research with recombinant DNA molecules throughout various sectors of our society only if some additional precautions can be taken and if the provisions of the NIH guidelines and their modifications can be legally enforced in an effective and practical manner.

In the meantime, the public debate must continue to confront the larger societal issues that have philosophical and ethical implications. Does the insertion of genes from higher organisms—as an example, mouse genes—into lower organisms—as an example, the bacterium E. coli—in itself constitute a dangerous breach of evolutionary barriers? Assuming that the genetic manipulations of human beings becomes a practical possibility, can we arrive at sane decisions that will protect the right of every individual to be different?

Our citizens committee has attempted to tackle questions such as these, and the answers to them are not quantifiable. The responsible citizen then turns to the experienced scientist for some reassurance on more technical questions. But it is not very reassuring to be confronted by conflicting statements from among the experts themselves—statements that leave wide gaps in a logical argument. For example, the public is to gain confidence from the fact that mutant strains of the bacterium E. coli will be prepared that, among other factors, survive best at 30° C and would therefore not survive well if they found their way to a human host with a body temperature of 37° C. At the same time, we are being told by some that certain bacteria that live in the soil would not be good alternate host organisms to E. coli for carrying out these experiments because tampering with the bottom of the food chain might lead to greater threats to our biosphere. The next logical inference, however, points to the realization that a mutant E. coli strain that survives better at 30° C than 37° C is in fact better adapted to survive in the soil. Thus we may be faced with the self-defeating process whereby eliminating one problem creates another still larger problem. As another example, we are being told that mutant bacterial strains that might be released into the environment would have such difficulty in finding an ecological niche that, according to Darwinian theory of natural selection, they would not survive in the environment. Carrying this argument to its extreme would lead to the conclusion that evolution does not occur, which is, of course, contrary to scientific evidence. The difficulty in accepting the argument above lies in the fact that Darwinian natural selection is dependent on a particular environment. I have little confidence in society's ability to maintain an invironment constant enough to protect a wild strain of a particular species. The large increase of antibiotic resistant bacterial strains arising from the excessive use of antibiotics in recent years lends validity to this argument.

One can begin to recognize the magnitude of the uncertainties. To assign a probability value in order to evaluate danger may be better than no estimate at all, but to treat this as a meaningful number can only serve to give the public a false sense of security. A 10-milliliter sample of culture contains an average of about 10 billion bacteria. A

ment freedoms. If we have freedom of speech, does that not entail freedom of thought?

I would hope that most people would generally follow the practice of thinking before they speak, and this does raise some interesting legal questions as well as scientific ones.

I do want to commend you for your statement. I also would like to concur in your views that a diverse panel would be a more appropriate vehicle than a science court to resolve those issues which must be resolved.

The problem with an adversary proceeding is that it develops upon the premise that one side is right and the other side is wrong, and does not permit the possibility that both sides are partly right and partly wrong.

Again, I would like to come back in more detail with some questions following the presentations by the other panelists. I'm looking forward to a very constructive dialog.

We will next ask Mrs. Hessy Taft of Princeton, N.J. to present her testimony.

[Biographical sketch of Hessy L. Taft follows:]

HESSY TAFT

I was born in Berlin, Germany, lived in France and Cuba as a child, immigrated to the United States in 1948 (age 14) and became a naturalized U.S. citizen in 1954.

I graduated from Barnard College with a major in chemistry and I hold an M.A. degree in chemistry from Columbia University.

For eight years I worked in biochemical research laboratories at the Downstate Medical College of New York, at the Rockefeller Institute and at the Rutgers University Institute of Microbiology and Medical School.

In 1967, I joined Educational Testing Service where I have major responsibility for the development of chemistry tests for college admissions, credit and/or placement as well as the development of general science tests and science evaluation instruments on the elementary and secondary school level both in this country and abroad. In 1976, I was involved in a project for the Federal Energy Administration that required holding hearings on the status of energy education.

Since 1965, I have prepared abstracts from recent research articles in biochemistry (in English, French, Spanish, and Italian) for publication in "*Chemical Abstracts*" for the American Chemical Society.

Other publications include:

1964—*Journal of Biological Chemistry*, 239.4041 (1964). "Metabolism of Inorganic Pyrophosphate."

1977—*Energy and Power Journal*, March 1977. "Analysis and Interpretation of In-School Energy Education."

Professional affiliations include the American Chemical Society, the National Science Teachers Association and the American Association for the Advancement of Science.

I am currently a member of the Princeton Citizens' Committee on Biohazardous Research appointed by the governing bodies of Princeton Borough and Township, whose charge it is to consider the issue of recombinant DNA research in our community.

STATEMENT OF HESSY TAFT

Mrs. TAFT. Thank you, Mr. Chairman.

I welcome this opportunity to appear before this subcommittee and to participate in some manner in the legislative mechanism that provides for such direct dialog between the citizens of this country and the elected representatives in our democratic system.

I am employed by Educational Testing Service, where I have the responsibility for the development of chemistry tests for college ad-

The board called for the creation of a local biohazards committee comprised of the Commissioner of Public Health, the chairman of the City Health Policy Board and three citizen members. This committee is responsible for reviewing all proposals for recombinant DNA research to be conducted in the city for compliance with its regulations.

The Cambridge Review Board did not see its work as preempting the enactment of national legislation. On the contrary, it recommended to Congress that uniform Federal guidelines be established to regulate all phases of the use of the technology. The board was clearly dissatisfied with the extent of Federal initiative in evaluating some of the potential risks. Prominent among its recommendations was that agencies funding recombinant DNA research require a health monitoring program designed to determine that survival and escape of laboratory organisms.

SIGNIFICANCE OF THE CITIZEN REVIEW PROCESS

The Cambridge Review Board tried to capitalize on the metaphor of a citizen court. It enabled citizens to raise issues about where justification rests, whether there is a presumption of danger, whether the controversy was over a conflict of rights, that is, the rights of scientific freedom of inquiry versus the rights of a community to protect its health and welfare, or whether a cost-benefit assessment was appropriate.

But the potential for embodying that metaphor into a structure was not fully exploited. A citizen courtlike process could have worked more effectively if:

(1) The process of educating members of the board were carried out more systematically. As it turned out, the education of board members was carried out concurrently with the inquiry process and without careful forethought. The Board's education of the technical issues was, for the most part, a responsibility of each member.

(2) The citizens made more extensive use of the adversary model for discovering the locus of the controversy. It could have benefited from more direct interchange between scientists.

(3) There were surrogate questioners who were skilled at eliciting information from technical people giving testimony and if these questioners were technically competent in the field in question.

There has been some discussion in science policy circles of a science court that could render a judgment on technical controversies that bear upon public policy. On this court would sit a select group of scientists who bear no vested interests in the outcome of the debate. Such a court of scientific elites would be responsible for sorting out the value and policy issues from the factual disagreements and offer their assessment to policymakers. It is my contention that this would have been impossible to carry out in the recombinant DNA controversy. There was no single body of fact or theory relevant to the assessment of risk that all scientists agreed upon. There was divisiveness on the replicability of experiments, the interpretation of data, the adequacy of criteria, the potential for emergence of novel properties and what information was relevant to resolve controversial areas. Given that a group of scientists could not divide up the issues of fact and value, and

Dr. Krimsky served on the Cambridge Experimentation Review Board from August 1976 through January 1977. The citizen board was established to review the potential hazards of having a P-3 laboratory facility in Cambridge for doing recombinant DNA research.

STATEMENT OF DR. SHELDON KRIMSKY, ASSOCIATE DIRECTOR, PROGRAM IN URBAN, SOCIAL, AND ENVIRONMENTAL POLICY, TUFTS UNIVERSITY

Dr. KRIMSKY. Thank you, Mr. Chairman.

I am pleased for this opportunity to share with you some thoughts I have about the significance of a unique experience in citizen participation and local initiative. From August 1976 to January 1977 I served on the Cambridge Experimentation Review Board, a citizen committee created to advise local officials on whether recombinant DNA research should be permitted in the city. My brief remarks this morning will be directed at three areas:

1. What the process was like;
2. What the outcome was; and
3. What the significance of that process is to other areas of citizen involvement in scientific and technical decisionmaking.

THE PROCESS

From my vantage point the city would never have challenged the universities on the appropriateness of a P-3 containment facility in a densely populated area were it not for a small vocal group of socially responsible scientists and technicians. These people, like so many other advocates of a minority position regarding public welfare, were prepared to accept ridicule from their colleagues and superiors and possibly setbacks in their careers.

If we want to insure that future controversies of this type get a public airing, we must encourage dissident scientists to speak out, not just to their colleagues in specialized fields but to a public forum. It's not comfortable for many scientists to accept that role. We must continue to remove the obstacles that inhibit people of good will from speaking out about their fears of certain research or the inadequacy of laboratory safety standards. Two things that come to mind in this area are: (a) decentralized science, since science that's hierarchical would provide an additional impediment for encouraging scientists to speak out; and (b) education, the promotion of curricula in the early training period of scientists that explore issues of scientific responsibility to the public. Moral deliberation of such issues should not await the time scientists are in a compromising situation.

A Cambridge experimentation review board was authorized to study recombinant DNA research when the deep divisions in the scientific community were reflected in the city council. The city manager selected a group of citizens who had no formal ties to the universities proposing the research. Furthermore, the citizens had no special expertise in the field under review. As a result the "empathy factor" that is, the concern that the institutions proposing the research might lose valuable funds or that qualified researchers would leave in the event of a ban, was never an issue in the deliberations. When a newspaper article quoted a Cambridge scientist as saying that the best talent would

reacted in our strictness. That is to be preferred, I think, until knowledge comes along to suggest otherwise.

Mr. THORNTON. Dr. Johnson, I want to thank you again for your excellent testimony, and Mr. Holt, for your attendance here. To the earlier witnesses, let me say that we appreciate your contribution to the hearings of this subcommittee.

We will resume hearings at 9 a.m. on May 3 in hearing room 2318 for the purpose of discussing local actions concerning DNA recombinant molecule research. Thank you very much. This hearing is adjourned.

[Whereupon, at 12:10 p.m. the subcommittee adjourned to reconvene at 9 a.m., May 3, 1977.]

might well have to be developed to even take a look at this sort of thing. I think the NIH really was not in a position to speak substantially in this area because there is no experience and a lack of technology.

Mr. THORNTON. Of course there has been a lot of genetic engineering going on in agriculture.

Dr. JOHNSON. Absolutely, but not using recombinant DNA technology.

Mr. THORNTON. That gets to the next point that I would like to get some further discussion on the record about. The different tools of research, that to me as a layman all look very similar, although maybe some of them occur naturally and some of them can occur only in a laboratory, might have the same effect. For instance, isn't one tool of recombinant DNA research to use a virus as a vector to go into one organism and over a period of time, to pick up genetic information there to be transferred. Then that altered virus is inserted into something——

Dr. JOHNSON. A gene is extracted from it and inserted into the virus, and the virus goes back to the host.

Mr. THORNTON. The virus penetrates the wall of the cell?

Dr. JOHNSON. That is correct.

It is really the same approach as in the bacterial work that has been going on so far, when they may use a phage which is a bacteria virus as opposed to an animal virus.

Mr. THORNTON. The ability of the virus to pick up genetic information from one host and then transmit it to another would seem to me to occur naturally as well as under laboratory conditions, am I mistaken about that?

Dr. JOHNSON. I do not think you are mistaken in theory.

I think the evidence for whether it has in fact happened is not documented, but in theory I think that is quite correct.

I think, for that to happen very frequently, there would have to be some evolutionary advantage, probably, for the virus to pick up that information. I am not aware of good documentation of that, but in theory I think it is quite possible.

Mr. THORNTON. By contrast with that, there are direct insertions, I believe, by breaking down the cell wall and separating the molecular information, the DNA chains, and then inserting a plasmid into that chain.

Dr. JOHNSON. Yes.

Mr. THORNON. This is more of a manipulative type of operation, it seems to me.

Dr. JOHNSON. Correct; the results, if you assume in the former case that it happened, the result would not be radically different, which is what I think you were getting at.

Mr. THORNTON. What I am saying is that you achieve about the same results, using a different tool of research. We were told earlier in these hearings that one of the experiments which had caused a great deal of concern, the development of an oil-eating bacteria, was not a recombinant DNA research item at all.

Dr. JOHNSON. That is correct.

Mr. THORNTON. Was it a totally different process which would technically not be included under the NIH guidelines on recombinant DNA?

Dr. JOHNSON. I hope you will not ask me to comment on that.

Mr. BROWN. You should have been here last night—the reaction of the Congress and the general public is going to be basically different, because they are going to see——

Dr. JOHNSON. I experienced that at the National Academy of Sciences Forum, actually.

Mr. BROWN. Because they are going to see this task as operating on the verge of man's knowledge. They are going to give much more weight to the uncertainty and lack of knowledge than to what we really know.

Dr. JOHNSON. But my point is that you can make careful assessments based on what we know. And we know a great deal about *E. coli*, and we know a great deal about antibiotic resistance and its mechanisms and we know a great deal about how to assess pathogenicity.

There are subjects being introduced in this controversy which, in my opinion, have nothing to do with recombinant DNA in scientific discussions. These include classing people. But there is certainly no intent to do that and if that sort of thing was ever to happen, I would be in the trenches and on the ramparts with everyone else, because I think that is an unreasonable thing to do.

Mr. BROWN. There are a lot of people who think that we have a gene that gives us knowledge of good and evil, and if we get the wrong kind of research going on, it will transmit that gene so that it does not recognize good but only does evil.

Dr. JOHNSON. I think you have to examine the incentives and the reasons for doing some of this research. In industry our reasons and our incentives are pretty well defined. It is to make a useful product and I just do not think that some of these projects are particularly pertinent to this subject.

Mr. BROWN. I do not want to belabor this. But I mentioned to the earlier witness about the possibility of developing a strain of nitrogen-fixing bacteria that could be attached to corn or various other things, thus fixing directly from the atmosphere a good part of what the chemical industry now provides in nitrogen fertilizer. This does two things. It has a pretty serious impact on the chemical business, and it may even destroy it, and favors the pharmaceutical business which makes these new kinds of nitrogen-fixing bacteria.

On the other hand, it introduces a mutant strain of bacteria into a very complex ecology with the soil bacteria. Do we have the capability to know what will happen when we introduce mutant strains into a complex ecology? Have we tried to assess this?

In the kind of problem that I am trying to speculate about, how much knowledge has been gained?

Dr. JOHNSON. I cannot really speak to how much analysis has been made. I certainly share your concern that the impact on the environment and on evolution and things of this sort should be seriously considered. I come back to the point, I think that it can be assessed very carefully, that you can make rather accurate predictions of probabilities.

I would also say that many of the things that have been associated with possible recombinant DNA research have not been attempted. All the work that has primarily gone on so far, any place in the world, has been with bacteria in the laboratory. And whether, in fact

Dr. JOHNSON. The question I asked a member of the GMAG Commission was whether they were receiving industrial protocols and whether industrial research was going on.

He indicated that they were and he did not see any problem with it. He did not mention the matter of sanctions to me.

Mr. THORNTON. I think perhaps the road that they took was to go forward with standards and to encourage work, but in addition, to assess rather strict penalties for noncompliance.

Dr. JOHNSON. That is inherent in this policy, that is correct. I was unaware that any sanctions had been applied, however.

Mr. THORNTON. I am relying entirely, as it turns out, on my recollection of witnesses' testimony at earlier hearings. It may not have been England that had adopted those sanctions, but it is my recollection that it was.

Mr. Brown, do you have any questions?

Mr. BROWN. Just a couple, Mr. Chairman.

I also want to commend Dr. Johnson on his statement.

I note your description on page 3 of the efforts that you made to involve your employees and the public in the fact that you were moving ahead in this area. We have grappled with the problem here in Congress of how to get public involvement and participation in certain kinds of decisionmaking processes.

I wonder if your effort was a conscious effort to develop this involvement as a means of attempting to alleviate future problems. Do you have a specific plan or reason in mind for this rather elaborate effort to inform your company employees and the public as to what you were doing in this case?

Dr. JOHNSON. I certainly think we had a responsibility to inform our employees and within limits of proprietary interest, to inform the public. We were certainly stimulated by the controversy over this area. I would not be candid if I did not admit that.

Mr. BROWN. At some point in the organization you decided to do this. In discussing it, did you say to yourselves:

If we do not do this, we may get a reaction in the community like they had up at Cambridge, and we ought to take this positive action to alleviate that kind of a problem?

Dr. JOHNSON. I do not think that was really our motivation. We were certainly aware of that. We keep our employees, for example, informed about what we are doing at all times, within certain limits. And we have always had extremely good relationships with our community and we have never hidden what our intents were in any of our areas of research, again within the limits of proprietary information.

Mr. BROWN. This is a very common, generic kind of a problem.

Dr. JOHNSON. I understand that.

Mr. BROWN. I am interested in the responses. For example, the chairman sometimes fails to tell me what he is planning to do.

[Laughter.]

Dr. JOHNSON. Do you think that is a conscious plan, Mr. Brown?

Mr. BROWN. I wonder. There is another generic aspect of this problem that I wonder if you could comment on. I have been frankly impressed with the considerable effort that scientists involved in the field, whether employed in Government, universities, or private indus-

Mr. THORNTON. I want to thank you for a very well-organized and well-prepared paper and testimony, and to express my appreciation for the additional material which you have related to us as you went through this statement.

Our distinguished minority member, Mr. Hollenbeck, had to leave just as you completed your statement in order to take his son to catch an airplane. He asked me to commend you for the statement and to request that he be given an opportunity to submit questions in writing to you to be answered.

I would like to extend that request on behalf of myself and other members of the committee as well. Would you be agreeable?

Dr. JOHNSON. Certainly.

Mr. THORNTON. At the risk of overstepping slightly, I note that our earlier witnesses are still in the room, and I wonder if they would be agreeable to responding to such written requests as may be addressed to them by the committee.

Dr. ADAMS. Certainly.

Mr. THORNTON. I think it might be appropriate a little later, after we have analyzed a couple of points in this testimony, to provide some opportunity for an exchange of views among all of the witnesses here. If Dr. Adams and Mr. Brennan are intending to remain on hand, we might ask them to come back up to the table a bit later.

I was concerned about what I trust was an inadvertent omission of your participation in the Asilomar conference. It does seem to me that it is important to any consideration of scientific research and prospective regulation of that research to recognize that some of that research is carried on in our university, and is under Federal assistance programs. But it is also carried on by the private sector, and all segments should be involved, along with the general public, in making policy determinations.

Dr. JOHNSON. I do not want to overstress my concern about that matter. Events in those days were moving very rapidly. As I indicated in my testimony, I may well not have approached it properly and I approached it on an informal basis to a member of the organizing committee.

I should have perhaps done it more formally, and I should perhaps have approached more people. I did not.

Mr. THORNTON. As I indicated, it may well have been inadvertent, and just a chance happening.

Dr. JOHNSON. I think that is very possible. I mentioned this to Dr. Singer and she indicated that Dr. Berg was actually seeking independent industrial participation. We were not approached or invited, however.

Mr. THORNTON. I think it might be very useful for you to provide us with some help in establishing what different legal principles, guidelines, policy considerations might be applicable to the utilization of research, or commercialization of research products, as contrasted with the conduct of basic research.

Dr. JOHNSON. Production as opposed to research, is that the question?

Mr. THORNTON. I am trying, not necessarily to put them in opposition, but to distinguish between them. If you would tell us how you perceive the proper role of regulation and restraint with regard to those elements.

DeHoney's design chosen for credit union logo

"I've never designed a logo before," says Richard DeHoney (Creative Services). "It really was fun to work with." DeHoney designed the winning entry in the Eli Lilly Federal Credit Union logo contest.

When he heard about the contest, DeHoney recalls that his first inclination was not to enter it, principally because he assumed that there would be numerous entries. He was right. But entries were submitted by 205 different employees. After the thought that the new, federally chartered credit union really needed a logo, kept occurring to him, and he decided the project would be interesting and to tackle.

DeHoney worked with several ideas at first. The one he chose for further development, which eventually became the winning entry, symbolizes what he thought the credit union's slogan should "say."

"Our credit union is growing — it's on the move," he says. "So I felt that the logo should be something contemporary." DeHoney points out that diagonal lettering has become very popular in the 1970s, thus making it appropriate for an expanding credit union's logo. "At the same time," DeHoney says, "I thought the logo should suggest continuity and there's the reason for the repeat in ending pattern."

Alice Oliver, IMC-Elizabeth Arden product evaluation-sel, chairman of the seven-member logo committee, reminds that the judges "had a difficult job in picking a winner from among the many clever and varied entries. The response was fantastic," she says. "We had no idea so many people would participate when we announced the contest."

Oliver says that simplicity and visual impact were the criteria that the judges looked for. She emphasizes that the concept, rather than artistic ability, was the basis for choosing the winner.

DeHoney has received a $100 savings bond as his prize.



The winning logo chosen from 205 entries, symbolizes "continuity, continuity" in the words of its designer.



Richard DeHoney — his creativity overflows to the credit union's new logo, too.

Personnel changes



John S. Emmerson, Ph.D. . . . from head of metabolism . . . to director of toxicology studies

William B. Gibson . . . from head of toxicology . . . to director of toxicology planning

Dale E. Kant . . . from director of finance, Eli Lilly International Corporation . . . to corporate controller, Eli Lilly and Company

Wilbur A. Lewis . . . returning to Indianapolis from Elizabeth Arden, Inc. (New York), to become personnel director

John J. Renck . . . from personnel director . . . to executive director, industrial relations

Robert A. Warwick . . . from assistant corporate controller, Eli Lilly and Company . . . to director of finance, Eli Lilly International Corporation

Other changes:

Emerson B. Houck . . . from personnel director . . . to corporate personnel director for Elizabeth Arden, Inc., retaining responsibility for corporate recruitment



Evans



Wilmot



Emmerson



Gibson



Kant

RESCREEN & SQUARE HALFTONES

Johnson discusses DNA research

(continued from page 1)

to jump the species barriers and recombine naturally occurring DNA in virtually any way they choose.

Most of the work thus far has involved the insertion of foreign DNA into bacteria. In theory, however, scientists could introduce DNA from any source into cells from any plant or animal. Genetic recombinations in the laboratory aren't entirely new, of course. They've actually been done for several years now through a less precise technique called cell fusion.

How is foreign DNA inserted into a bacteria?

Scientists have recently discovered a whole new class of enzymes that can cut and splice the long DNA molecules in specific ways. The compounds work with genetic material from any source. They are used to attach foreign DNA fragments to the DNA of either bacterial viruses or plasmids. The latter are bits of DNA that exist apart from the chromosomes in certain bacteria. Under the right conditions, plasmids and viruses have the capacity to enter the bacterial cell and then reproduce themselves once inside. When linked appropriately to a piece of foreign DNA, they will carry it into the cell and reproduce it along with their own genetic material.

What do you gain from this?

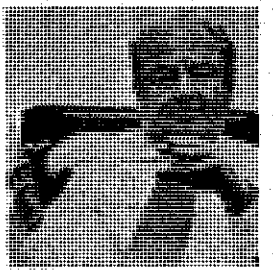
Well suppose, for example, that the foreign DNA fragment was the gene that codes for a specific hormone such as insulin. You might eventually develop a new strain of bacteria that could synthesize it directly. This could be much more efficient than the current system of extracting the hormone from the glands of animals. At the very least, it would supplement the supply available from animal sources.

There's a whole range of other possibilities, of course. Certain soil bacteria, for example, can convert atmospheric nitrogen into nitrogenous compounds that plants can use as food. If the gene group responsible for this process could be incorporated into wheat or other crops, they might eventually be able to pull their own nitrogen fertilizer out of the air.

The practical benefits sound fantastic. Does the technique have any applications in basic research?

Yes. And they're tremendously important. Recombination techniques, for example, can be used to map the chromosomes of an organism. This means to locate the specific gene or genes responsible for various functions such as photosynthesis or control of cell replication. When the gene of interest has been located, the same techniques can then be used to produce it in quantity for additional studies. The mapping of chromosomes will lead, almost inevitably, to new biochemical information about disease processes of all kinds.

DNA recombinations can also help us learn how cells turn their genes on and off in producing the endless array of compounds needed by the organism as a whole. Knowledge of this kind, for example, will probably be necessary before we can actually transform bacteria into little production units for antibiotics or hormones. The important point here, however, is the synergism that comes with new basic information. A clarification of gene control mechanisms, when combined with existing knowledge, could easily generate a totally new lead or insight in another area.



Great. But how about safety? Do the NIH guidelines really give adequate protection?

The majority of biologists feel that the guidelines, though conservative, are reasonable given the present state of our knowledge. This is the consensus among Lilly scientists also. We think conservatism is a good approach with research as basic and revolutionary as the first recombinations of genetic material. The restrictions will probably be moderated later as experience proves the potential dangers have been exaggerated.

What sort of dangers are people worried about?

The accidental creation and escape of new life forms that could harm either man or the environment. Most of the concern centers on virulent microorganisms for which there would be little or no immunity and that might also be resistant to current antibiotics. Some people also fear an increased survival capacity in the new organisms which, on escape, could allow them to gradually destroy other life forms and thus disturb the environmental balance. The vast majority of scientists, however, think both scenarios are very improbable and feel, in any event, that the guidelines will provide adequate protection.

Needless to say, Eli Lilly and Company fully supports the letter and spirit of the guidelines. We've had years of experience in dealing with pathogenic organisms and feel confident of our ability to work safely with DNA recombinations.

Could you give us a quick summary of the guidelines?

Yes. Their core objective, of course, is to keep the recombinant molecules in the laboratory. This is achieved through two kinds of containment, one physical and the second biological. The greater the theoretical risk of the experiment, the more stringent the rules of containment.

The levels of physical containment range from P1 through P4 with the latter requiring the most restrictive procedures. P1 calls for standard biological practices. P2 prohibits mouth pipetting and the creation of aerosols. P3 requires safety cabinets for all handling, negative air pressure in the laboratory to prevent airborne escape, and decontamination of lab exhausts. P4 specifies air-tight chambers for all handling, special clothing for laboratory personnel, and both airlocks and decontamination procedures for anything leaving the lab.

Biological containment is achieved primarily through the use of host cells that have little or no capacity to survive outside the laboratory. The more restrictive procedures require cells made genetically dependent on special nutrients rarely found in nature. The guidelines specify the physical and biological constraints that must be implemented with various combinations of host cell, virus or plasmid carrier, and foreign DNA.

Certain types of experiments, of course, are forbidden altogether. These include the transfer of foreign DNA that produces toxins and the introduction of genes for drug resistance into microorganisms not known to acquire them naturally.

The safety procedures sound elaborate. But what are Lilly's current research interests with recombinant DNA?

We're attempting, among other things, to use the new techniques with antibiotic-producing microorganisms. Our objective is to create modified organisms that can either synthesize new and better antibiotics or produce an existing one more efficiently. This kind of work isn't entirely new. Lilly and many other laboratories have been modifying organisms with chemical and physical agents for years.

Lilly also hopes to use DNA recombinations to produce hormones and other medically useful proteins. Some of the compounds we have in mind are simply not available in any significant quantity at the present time. With others, our main objective will be to produce them more efficiently.

In closing, Dr. Johnson, could you mention a few of the long-range possibilities from research with recombinant DNA?

Okay. But remember, the time frame on such things is impossible to predict. And many developments may never occur even though, from our present viewpoint, they seem almost inevitable. Scientific revolutions somehow never seem to produce all that's expected of them in their infancy.

Probably the most significant thing about DNA recombination is the enormous increase in basic knowledge it can provide. Eventually, for example, it could lead to a complete understanding, in strictly chemical terms, of pathologies such as cancer, heart disease, malfunctions of the immune system, and even the aging process itself. Knowledge of this kind, obviously, is our best hope for real progress in all these areas.

How about some of the more tangible benefits?

The theoretical possibilities — and, remember, that's all they are at present — sound like pure science fiction. Some of the things most frequently mentioned are: tailor-made microorganisms for energy production and pollution control; plants that are resistant to diseases, pests, and drought; a whole range of hybrid plants such as a "pomato" with tomatoes above ground and potatoes on its roots; beef cattle, swine, and poultry designed for taste and efficient production; completely new species of plants and animals; and, finally, cures for genetic diseases through replacement of the defective DNA.

None of these things is just around the corner. Some may not even be possible. Society as a whole may eventually find others undesirable. Nonetheless, it is time — in my opinion — to begin a cautious exploration of this revolutionary research technology that science has provided. The potential benefits are enormous and the risks, though somewhat indeterminate, can be assessed and managed by responsible scientists.

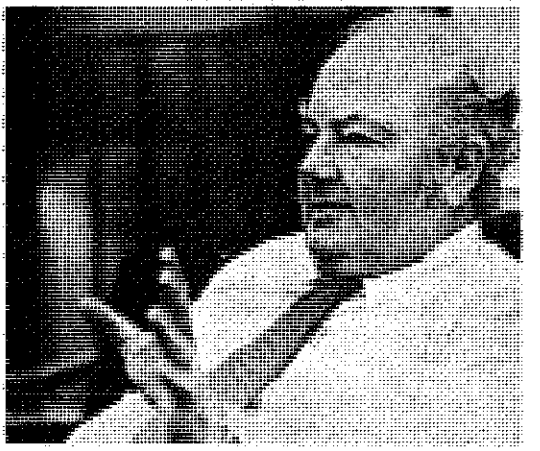
Facing page: DNA molecule — an artist's concept.

LILLY NEWS
VOLUME TWENTY-ONE, NUMBER THREE / APRIL 1977

Research with genetic recombinations generates promise and controversy

A new frontier has opened in biological science. Through a series of spectacular developments that date from the breaking of the genetic code in 1951, man now has the theoretical ability to recombine the genetic material from different species of plants and animals. This presents the great hope of altering these organisms in ways that are highly beneficial to mankind. Yet it also raises the question of risk, of the potential for negative effects from scientific procedures that have such far-flung application.

The possible risk from such research seems to vary greatly with the type of experiment. Thus, in 1974, American biologists called a moratorium on certain genetic recombinations until safety guidelines could be developed. The two-year moratorium ended last June when the National Institutes of Health issued its recommendations on the subject. Concern and, inevitably, some misunderstanding continue, however. Thus Congress is now holding legislative hearings on genetic recombinations and, in recent months, the news media have often discussed the benefits and possible risks from such research. To provide employees with background information on the general subject and also to explain the company's own research in this area, *Lilly News* presents the following interview with Irving S. Johnson, Ph.D., vice-president of Lilly Research Laboratories.



Irving S. Johnson

As a start, Dr. Johnson, could you give us a general idea of what's involved in this type of research?

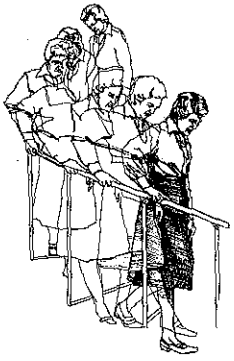
Well, first of all, genetic materials — chromosomes and their basic subunits called genes — are composed of deoxyribonucleic acid, otherwise known as DNA. All living things, with the exception of certain viruses, use DNA to both store their hereditary information and direct all of their normal life processes. It's DNA, for example, that makes a horse a horse instead of a man, a butterfly, or an oak tree. Slight chemical variations in DNA also differentiate individuals within a given species.

There is some natural exchange of genetic material between different species of microorganisms. This rarely happens among higher life forms, however, except on a very limited basis between closely related species. The importance of the new techniques in molecular biology is that they allow scientists

(continued on page 3)

More common form of disease affects 40 million

Nalfon approved for use in osteoarthritis



Nalfon®, the anti-arthritic prescription medication marketed by Dista Products Company, has been approved by the Food and Drug Administration for the treatment of osteoarthritis. Introduced in the United States in February 1976, Nalfon previously was cleared only for the management of rheumatoid arthritis.

Osteoarthritis is the milder — and more common — form of the disease. It affects an estimated 40.5 million Americans, or 37 out of every 100 adults. According to The Arthritis Foundation, 97 percent of all people over 60 years of age suffer symptoms of osteoarthritis. This form of the disease often begins relatively early in life — in the early 40s is typical — and earlier onset is not uncommon. Each year rheumatic diseases claim 250,000 new victims in this country.

In the United States, Nalfon is one of a new generation of non-steroidal arthritis drugs known as "profens" or "propionic acid derivatives" that has been cleared for use in patients with osteoarthritis. The major attribute of Nalfon and other propionic acid derivatives is their ability to relieve arthritic pain, reduce inflammation, and increase mobility with less chance of producing the serious side effects commonly associated with many of the other prescription drugs available for the management of rheumatoid arthritis and osteoarthritis. In most patients with osteoarthritis Nalfon has been shown to relieve arthritic pain after the first few doses. Patients taking Nalfon for as long as three years have demonstrated that it is well tolerated.

Anthony S. Ridolfo, M.D., head of research in arthritis and connective tissue diseases at the Lilly Laboratory for Clinical Research, emphasizes the importance of a physician's involvement in the management of an arthritic's disease. "It is important that persons with arthritis know that treatment by a physician often can bring relief and reduce or prevent disability," he says.

Nalfon was discovered and developed in the company's research laboratories in Indianapolis.

present state of our knowledge. This is the consensus among Lilly scientists also. We think conservatism is a good approach with research as basic and revolutionary as the first recombinations of genetic material. The restrictions will probably be moderated later as experience proves the potential dangers have been exaggerated.

What sort of dangers are people worried about?

The accidental creation and escape of new life forms that could harm either man or the environment. Most of the concern centers on virulent microorganisms for which there would be little or no immunity and that might also be resistant to current antibiotics. Some people also fear an increased survival capacity in the new organisms that, on escape, could allow them to gradually destroy other life forms and thus disturb the environmental balance. The vast majority of scientists, however, think both scenarios are very improbable and feel, in any event, that the guidelines will provide adequate protection.

Needless to say, Eli Lilly and Company fully supports the letter and spirit of the guidelines. We've worked safely for years with pathogenic organisms, such as the viruses responsible for polio and certain animal tumors. Thus, we feel confident of our ability to handle DNA recombinations without harming either our employees, the general public, or the environment.

Could you give us a quick summary of the guidelines?

Yes. Their core objective, of course, is to keep the recombinant molecules in the laboratory. This is achieved through two kinds of containment, one physical and the second biological. The greater the theoretical risk of the experiment, the more stringent the rules for containment.

The levels of physical containment range from P1 through P4, with the latter requiring the most restrictive procedures. P1 calls for standard biological practices. P2 prohibits mouth-pipetting and the creation of aerosols. P3 requires safety cabinets for all handling, negative air pressure in the laboratory to prevent airborne escape, and decontamination of lab exhausts. P4 specifies airtight chambers for all handling, special clothing for laboratory personnel, and both airlocks and decontamination procedures for anything leaving the lab.

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Certain types of experiments, of course, are forbidden altogether. These include the transfer of foreign DNA that produces toxins and the introduction of genes for drug resistance into microorganisms not known to acquire them naturally.

Dr. Johnson recently discussed recombinant DNA research before a public forum in Washington, D.C., sponsored by the National Academy of Sciences. He has communicated similar information to Lilly employees and has also been a frequent spokesman on the subject for newspapers, radio, and television. An active scientist for twenty-four years, he has published some sixty research papers in fields ranging from cancer chemotherapy and virology to heart cell function and the tissue-culture production of insulin.

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Most of the work thus far has involved the insertion of foreign DNA into bacteria. In theory, however, scientists could introduce DNA from any source into cells from any plant or animal. Genetic recombinations in the laboratory aren't entirely new, of course. They've actually been done for several years now through a less-precise technique called cell fusion.

the Far East to the wheat fields of Canada, and from apple orchards to vineyards. A major part of our animal work includes, as it has for many years, new compounds for improving the efficiency with which beef cattle utilize their feed, and antibiotics for controlling infections in poultry and swine.

Much further behind in the long sequence of research steps are ideas and projects that offer little more than interesting possibilities at the moment, but they do illustrate the imagination and diversity with which our scientists tackle their work:

* Interrupting the molting cycle of insects by inhibiting their internal production of certain enzymes

* The isolation and reproduction of living heart cells for testing cardiac drugs

* The relationship of humoral (circulatory) and cellular immunity in the body's natural defense against disease

* The role of metabolites in a drug's ability to act in the body

* Preventing the degradation of amino acids in the rumen of cattle to increase the animal's utilization of the protein in feed

* Influencing the brain's secretion of substances known to affect emotional state

* Increasing the production and "turnover" of cells in the outer layers of the skin

* The physiology of the metabolic processes related to obesity

* Shortening the required growing season for crops by speeding up their growth or delaying the maturing of crops to increase yields

* Speeding antibiotic production by improving the growth characteristics of the organisms that produce antibiotics.

I hope these few minutes have given you some insight into our research activities. Lilly scientific research is a singularly complex human endeavor. It means thinking things that have never been thought before, doing things that have never been done before. It means building knowledge, step by laborious step, using the powers of intelligence, technology, and organization to move from the hypothesis of the laboratory to the reality of better health and more food.

Research is more hard work than sudden inspiration, more questions than answers, more failures than successes. But the sweet taste of success is a powerful stimulant. As many Lilly people know, there is nothing quite like the special feeling that comes with a significant contribution to medicine or agriculture. I am confident that members of the Lilly research staff will experience that feeling as often in the future as they have in the past.

* The time, effort, and expense required are the greatest.

* The potential benefits to society are the greatest.

* The potential financial returns to the company are the greatest.

We balance this long-range strategy with important and complex, but shorter-range, projects related to modification of existing products, improvements in production yields, treatment of waste materials, and uncompromising quality standards.

Time and continuity are also essential ingredients of successful research. Progress should be measured in decades, not years. We test 8,000 experimental compounds before we find a marketable product; and it, of course, takes much longer to rule out the 7,999 than to find the one. This means the perseverance of scientists must be matched by the patience of shareholders! Time also creates continuity, which gives a research organization the vital, but intangible, characteristics of experience and teamwork.

Our final guideline concerns the systematic organization of effort. We believe that nothing is as precious or productive as the brainpower of an individual scientist. But coordination is a must, and for this reason we rely heavily on research project groups. There are more than 120 such groups. Here is a partial listing:

- Animal Physiology
- Animal Science Field Research
- Antibiotic Resistance
- Antimicrobial Growth Promotion
- Atherosclerosis and Thrombosis
- Bioavailability and Drug Absorption
- Cardiovascular Research
- Central Nervous System
- Cephalosporin Process
- Cyclic Nucleotides
- Drug Metabolism
- Endocrine Research
- Fermentation Products Microbiology
- Fermentation Products Screening
- Gram Positive/Antifungal Antibiotics
- Herbicide Research
- Immune Function and Connective Tissue Research
- Infectious Disease—Host Defense
- Insulin Biosynthesis
- Ionophore Research
- Metabolic Efficiency
- Mutagenesis/Carcinogenesis Screening
- Pancreatic Physiology
- Parasitic Helminths
- Plant Genetics
- Plant Growth Regulators
- Psoriasis Research
- Radioimmunoassay
- Recombinant DNA Research
- Rhinoviruses
- Rumen Fermentation
- Somatostatin Analogues
- Systemic Parasiticides
- Veterinary Research
- Vinca Modifications
- Virus Chemotherapy

Also we routinely screen virtually all compounds for several types of activities, even those quite different from original intent. Thus, in a year we will screen 8,000 compounds for possible effectiveness against as many as seventy-five biological targets, including such varied ones as malignancies, viruses, bacterial infections, insects, and weeds. We also check many of the same compounds as growth stimulants for animals or plants and growth retardants for other plants. It adds up to something over 150,000 individual screening tests per year. In short, we have set up the machinery to make a gross evaluation of large numbers of com-

THE CHALLENGES OF RESEARCH

an address by

Earl B. Herr, Jr., Ph.D.
President
Lilly Research Laboratories

Annual Meeting of Shareholders
of
Eli Lilly and Company

Wednesday, April 20, 1977
Lilly Center
Indianapolis, Indiana

Baseball's famous manager Casey Stengel once observed that the chief shortcoming of his star 300-hitter was that the gentleman failed to do anything useful seven out of every ten times he came to bat.

I hope you won't be disillusioned when I tell you that research scientists at Eli Lilly and Company—or anyplace else— would happily settle for a batting average only one one-thousandth as effective as Casey's star batter. The simple truth about our scientific research is that prodigious amounts of effort, money, and time are required to make satisfactory progress. The brilliant "breakthroughs" desired (and rather routinely expected) by the public are usually the culmination of thousands of failures and a few successes, over many years. We in research have never been quite so smart as nonscientists believe us to be.

Another bit of lore about research scientists has them constantly seeking the answers to baffling, but well-defined, questions. Once again, please don't be disappointed when you learn that good research scientists spend as much time trying to decide the right questions as they do looking for the answers.

November 2, 1976

Donald S. Fredrickson, M. D.
Director
National Institutes of Health
Public Health Service
Department of Health, Education, and Welfare
Bethesda, Md.

Dear Doctor Fredrickson:

The following comments are provided in response to the notice published on July 7, 1976, FR (41) 131 entitled "Recombinant DNA Research - Guidelines" by the Department of Health, Education, and Welfare.

As you know, the Pharmaceutical Manufacturers Association presented testimony before the Health Subcommittee of the Senate Labor and Public Welfare Committee on September 22, 1976. A copy of that testimony is enclosed. Also enclosed is a copy of our letter, dated September 29, 1976, in response to your request of September 7, 1976, for comments on patent policy considerations pertinent to government sponsorship of recombinant DNA research.

The general purpose of this letter is to reiterate our statement that PMA member firms support the spirit and intent of the Guidelines. As noted in our testimony, we believe that in the case of non-government supported research some modification will be necessary regarding (1) protection of intellectual property rights and (2) volume restrictions. It is our considered opinion that such modification can be achieved without harm to the purpose or effectiveness of the Guidelines. Such modification should be general rather than specific, and should provide for negotiations between non-government supported sponsors of such research and appropriate officials of your office.

One further example of industry's experience and capability is the production of mutant strains of bacteria and other microorganisms by X-ray and other mutagenic techniques in research designed to increase the yield of antibiotics and other drug substances produced by fermentation.

One must conclude from these examples and from the excellent safety record of the industry in research and production of other potentially biohazardous materials that it is well aware of the risks involved, and that it has the capability to avoid contamination or injury to its employees and to the environment. For PMA's part, we will exert every effort to keep apprised of our member firms' involvement in such research, and will encourage cooperation with the scientific community and other peer groups, including government agencies in adopting necessary controls.

It is too early to know the ultimate outcome of much of this research which has and will be undertaken. We might predict, however, that recombination of DNA in a host bacterial cell could produce quantities of medically needed natural products such as hormones and other important drugs by fermentation processes rather than by extraction of such raw materials as pancreas or other tissues of animals and plants.

Bacterial or other cultures of such recombinant DNA fragments could be maintained and propagated to serve as a constant and reliable source for production. New recombinant molecules might also serve as bases for new antibiotics or as a means to increase yields of existing antibiotics much in the same way now employed in the use of mutant strains. The application of this technology to basic research of the disease process - more specifically to genetically induced or associated disease - offers great promise.

The potential risks of recombinant DNA research and its commercial application are well recognized. It is perhaps unfortunate that the term has become synonymous with "genetic engineering", a concept which is most frequently associated with the manipulation of human genetics or with the deliberate creation of highly toxic or virulent new species of plant and animal cells. It is important, we believe, to emphasize that the present state of the art and the provisions of the NIH guidelines militate against research and development that would pose such a threat to society.

In the case of the drug industry, it is highly unlikely that research and development would involve organisms in Classes 3, 4 and 5 as established by the Office of Biosafety of the Center for Disease Control of the U. S. Public Health Service in its publication entitled "Classification of Etiologic Agents on the Basis of Hazard" or that adequate biological containment procedures would not be available. Many of our member firms now routinely use P-1 and P-2 physical containment facilities in their research operations and it is not uncommon to find facilities in the drug industry that correspond very closely to the specifications for P-3 levels of containment. At least one of our firms is now constructing a P-4 facility.

Statement on Recombinant DNA Research
On Behalf Of The
Pharmaceutical Manufacturers Association
Before The
Attorney General
State of New York
October 21, 1976

I am John G. Adams, Vice President of the Pharmaceutical Manufacturers Association, an organization composed of 130 members that discover, develop, manufacture and market most of the prescription drugs and a large percentage of the diagnostic reagents and medical devices available in the United States.

My testimony will be brief, but I hope responsive to your inquiry into the involvement of PMA member firms in recombinant DNA research. It will outline our views on the guidelines recently published by the National Institutes of Health.

The subject of today's hearings is one which is recognized by all elements of the biomedical research community as a major breakthrough along the frontiers of science. As an institution engaged in biomedical research, the drug industry is acutely aware of its scientific, moral and social responsibilities in this new field of research and development. It is for this reason that we are pleased to appear before you today and offer comments in support of a developing public policy that hopefully will maximize benefits and minimize risks.

I have attempted, in preparing for the hearings, to assess the extent of the activity of our member firms in this pioneering area. The responses revealed that all of the major research-oriented pharmaceutical firms (about 30) are very much interested in it but that only a few are now actively engaged in recombinant DNA research.

I am sure it will be clear from my remarks that the drug industry endorses the spirit and intent of the guidelines recently proposed by the National Institutes of Health. With some minor modifications, it is our opinion that the drug industry should and will accept the guidelines as an affirmative and constructive approach.

As you know, the prescription pharmaceutical industry is very heavily involved in general and biomedical research. Our member firms have demonstrated a high level of sophistication in their research and development programs as their record of innovation and accomplishment clearly shows. It is not surprising, therefore, that scientists in the drug industry are generally well aware of the pioneer work in DNA research which led to the discovery that DNA fragments bearing dissimilar but important genetic information, could be recombined in a host cell to create hitherto unknown genetic species.

In addition, we support the concept developed by the Department of Health, Education, and Welfare of providing the first option to ownership of inventions made in the performance of government research to those nonprofit or educational institutions having demonstrated technology transfer capabilities. The HEW's Institutional Patent Agreement has proved to be an effective means of encouraging commercialization of the results of Government-funded research. Therefore, we believe the IPA concept will assist in recognizing both the incentives of the United States patent system and the capabilities of the private sector in commercializing the results of Government-funded research. We recommend the continued full application of this concept to Government-funded activities in the area of recombinant DNA research. We see no valid reason for instituting a separate set of rules for such activities. Any potential safety factors associated with such research can adequately be addressed without alteration of the basic arrangement of private ownership of incentive subject matter under the limitations outlined in the IPA.

Your letter raises the concern of whether reliance upon the United States patent system may discourage the rapid exchange of research information within the scientific community. In our view, the opposite is true -- that is, elimination of the patent system in this area of research would serve to discourage rapid dissemination of information, either through private sector reliance upon trade secret protection or a reluctance by Government granteea to make full disclosure in reporting research results to the Government. Continued reliance upon the incentives of the United States patent system, through the mechanism of the Standard Institutional Patent Agreement, will encourage prompt reporting and the dissemination of information on research activities in the field of recombinant DNA. Therefore, we agree with the conclusions of your patent experts to the effect that there will be no undue burden on disclosure due to reliance on patent protection. In fact, we feel that the greater the reliance on the patent system the greater will be the incentive for prompt dissemination of private and Government-funded research results.

Your letter lists five options which may be appropriate means of allocating invention rights to Government grantees. In our view, the first three options are unacceptable in that patent incentives would not be utilized to an appropriate extent. We recommend that the Department continue to permit qualifying institutions to exercise the first option to ownership under the IPA. However, the Department should request that IPA grantees license only those institutions which are willing to conduct their DNA research activities in a manner consistent with Federal Government guidelines governing such research. Thus, we recommend a modification of your options 4 and 5 under which the grantee institution would license only those concerns

Report of The President's Biomedical Research Panel

The Congress has already investigated the problems of protecting proprietary information under the "trade secrets" exemption of the Freedom of Information Act [5 U.S.C. 552 (b)(4)]. The unpredictability of protection of proprietary information under the "trade secrets" exemption was discussed at length during consideration of the amendments to H.R. 3474, the Energy Research and Development Administration (ERDA) authorization bill for fiscal year 1976 [*Congressional Record*, H 12374-81]. Of special importance is the agreement arrived at between Congressmen Goldwater (R. California) and Moss (D. California) as set out on page H 12379, the essence of which appears in paragraph (6):

> We agreed that, in light of the apparent state of unpredictability of protection of proprietary information under Exemption (b)(4) and the need for ERDA to provide such predictable protection in order to ensure the full cooperation and participation of the private sector, Congress could conclude that there was a legitimate national interest in ERDA's having the specific authority to predictably protect proprietary information. Further, Congress could strike a reasonable and acceptable balance of that national interest and the national interest in freedom of information and create a (b)(3) exemption for ERDA for that purpose.

In December 1975, the Congress amended the Federal Non-nuclear Energy Research and Development Act of 1974 to provide positive and predictable protection for trade secrets and other proprietary information. In commenting on the provision, Senator Fannin (R. Arizona) stated (*Congressional Record*, H 12374):

> The conferees took this action because . . . under existing law, primarily the Freedom of Information Act, court holdings have made government protection of trade secrets and other proprietary information completely unpredictable . . . Our action here is intended to remedy that situation for ERDA. Our national energy research and development efforts are far too important to allow such an impediment to exist.

The Panel is not in a position to determine whether the existing laws as interpreted by the courts actually do, in effect, narrow congressional and court interpretations of the constitutional safeguards to intellectual property rights.

improves weight gains in poultry and swine, and controls a number of other diseases in cattle, swine, poultry, dogs, and cats.

Cordran®—Cordran, a corticosteroid for external application, alleviates itching and inflammation associated with various skin diseases.

Drolban®—The second anticancer agent introduced by Lilly is a synthetic steroid for the treatment of advanced breast cancer.

1963 Dymid®—A selective herbicide of major value to tomato growers, this product of Lilly discovery permits mechanical harvesting. It also is used to control weeds in peppers, potatoes, peanuts, and several other crops.

Oncovin®—The second anticancer agent to be developed from the periwinkle plant, Oncovin is used for the treatment of acute leukemias in children. It is one of more than 40 alkaloids obtained by Lilly phytochemists from the flowering shrub.

Treflan®—The discovery and development of Treflan gave the American farmer his first dependable weed-control agent. Treflan led the way to a new method of herbicide application for more than 40 crops including soybeans and cotton.

1964 Dymelor®—This oral sulfonylurea drug was discovered and developed for use in the stable, maturity-onset, nonketotic type of diabetes not controlled by dietary regulation alone.

Keflin®—An antibiotic of low toxicity, Keflin was the first agent to be developed from the cephalosporin family of antibiotics pioneered and developed by the company. Its synthesis was possible after a Lilly breakthrough in chemistry that provided as "raw material" the nucleus of the British-discovered antibiotic cephalosporin C.

Aventyl® HCl—Aventyl HCl is an effective agent for the treatment of mental depressions.

1965 Balan®—Discovered and developed as a season-long herbicide, Balan is used widely in the United States on lettuce, peanuts, alfalfa, tobacco, and other crops.

1967 Zonal Gradient Centrifugation—The first commercial application of the zonal gradient centrifuge for the purification of viral vaccines was pioneered by the Lilly company in preparing influenza vaccine. The ultra-high-speed centrifuge separates out most of the vaccine impurities, reducing the side effects.

1968 Proinsulin—Discovered by Steiner, of the University of Chicago, and first isolated in the Lilly Research Laboratories, proinsulin—the precursor, or forerunner, of insulin—is converted by body enzymes to insulin itself. The first determination of its chemical structure was an achievement of Lilly research.

1969 L-Asparaginase—Lilly scientists isolated and crystallized pure L-asparaginase, an enzyme found to be useful in the treatment of certain types of leukemia.

1971 Keflex®—Keflex was the fourth antibiotic of the cephalosporin family to be approved for marketing in the United States. It is an oral product used for treatment of respiratory, urinary-tract, skin, and soft-tissue infections.

Coban®—The company discovered and developed Coban, a unique anticoccidial agent for broiler chickens. Added to the feed, this fermentation product provides a truly new coccidiosis preventative to the poultry industry. Coccidiosis is a disease caused by infection with protozoan parasites.

1972 Paarlan®—Discovered and developed by Lilly, Paarlan is a pre-emergence herbicide for season-long control of weeds and grasses in flue-cured to[illegible]co.

1973 Kefzol®—Kefzol was the fifth cephalo[illegible]orin antibiotic to be marketed in the United States by [illegible]e company. It is an injectable product used for treatment of several types of serious infections including those of the respiratory tract, genitourinary tract and the skin and soft tissues.

1974 Surflan®—Surflan is a surface-applied herbicide used for soybeans.

Spike®—Spike is a Lilly-developed, surface-applied pre-emergence and postemergence herbicide for total vegetation control. This product has proven to be extremely useful along railroad rights-of-way and on industrial sites.

Year*	Accomplishment
1923	Iletin®—The first commercial insulin preparation for the control of diabetes was made available by the Lilly company after Banting and Best, of the University of Toronto, discovered the hormone insulin's role in the disease. With insulin, diabetics lead normal and productive lives.
1925	Amytal®—More than 100 barbituric acid derivatives were synthesized in the Lilly Research Laboratories to bring to the medical profession Amytal and Amytal® Sodium, which became especially important in surgery and obstetrics. These were the first of a series of barbiturate sedatives and hypnotics.
1926	Ephedrine—Widely used for the treatment of allergy, ephedrine was first introduced by the Lilly firm. It was derived from the stems of mahuang, a plant that had been used in China for its therapeutic value for more than 5,000 years.
1928	Liver Extract—Pernicious anemia was a fatal disease until liver extract was developed by the company in association with Minot and Murphy.
1930	Merthiolate®—An antiseptic, Merthiolate is particularly distinguished by its demonstrated low toxicity. It provides sustained activity against common bacterial and fungal pathogens, is relatively nontoxic and nonirritating to body tissues, and maintains activity in high dilution.
1933	Metycaine®—This anesthetic, developed by Lilly, has a more prompt, intense, and lasting effect than anesthetics previously available. It was the first anesthetic used for continuous spinal block for labor pain.
1934	Cyanide Poisoning Antidote—The standard treatment for cyanide poisoning was developed.
1935	Ergotrate® Maleate—Ergot has been used for centuries to induce labor and control postpartum bleeding. Before Ergotrate was developed by the company, physicians were handicapped by the instability and variation in potency of the ergot extracts available for their use. Ergotrate provided them with a stable drug inducing a predictable response.
1936	Seconal®—Seconal, a short-acting barbiturate, is prescribed for general sedation.
1937	Protamine, Zinc & Iletin®—The addition of protamine and zinc to insulin lengthened and controlled its action, permitting certain diabetics to reduce the number of daily injections required. In later years, other improved, modified insulins, including NPH and Lente®, were investigated and marketed. Nicotinic Acid—Discovery of the use of nicotinic acid for treatment of the diet-deficiency disease pellagra was an accomplishment of Lilly research.
1939	Angiotensin—In cooperation with investigators from Argentina, Lilly scientists discovered angiotensin, a powerful pressor factor, which has an important role in hypertension.
1942-1946	Wartime Accomplishments—During World War II, the Lilly firm was one of nine pharmaceutical manufacturers chosen by the federal government to manufacture penicillin for the armed forces. In addition, the company participated in a cooperative program on the determination of the structure of penicillin. . . . Also in the war years, Lilly scientists were deeply involved in the government-sponsored program concerned with the preparation of dried blood plasma and blood protein fractions to be used as blood extenders.
1947	Methadone—A potent analgesic and antitussive was marketed by Lilly under the trademark Dolophine® Hydrochloride. In March, 1973, methadone was approved for heroin detoxification.
1948	Penicillin Precursors—A significant achievement after penicillin's discovery came when Lilly biochemists found that the addition of chemical compounds to the penicillin fermentation greatly increased the production of penicillin G. Ultimately, this led Lilly scientists to produce other new penicillins. Duracillin® A.S.—After numerous attempts were made

*For new products, year is that of U.S. introduction. For scientific research achievements, year given is that of successful completion.

Interagency Task Force recommendations, we feel research projects should be registered. We do not feel they should be subject to prior approval.

The legislation should further provide for the issuance of regulations. These initially would be the NIH guidelines with necessary amendments. The legislation should also provide for inspection of facilities, for reporting requirements, and, as noted above, for the protection of confidential data.

In our view, the results of recombinant DNA research should not be subject to special patent restrictions. It is our understanding that the Committee will examine patent questions associated with this work at a later date, and we will forward comments to the Committee in conjunction with that hearing.

We trust the foregoing comments have been of assistance to the Committee and will be glad to respond to questions.

Respectfully submitted,

ELI LILLY AND COMPANY

(4) The work we have been engaged in at Lilly involves organisms which do not produce disease in man, such as streptomycetes.

(5) Work with disease-causing agents has been forbidden by the guidelines, and we feel these guidelines have been followed by the scientific community. There appear to be no practical benefits or medical reasons to work with organisms in those categories prohibited by the guidelines.

(6) Adherence to the guidelines should result in safe procedures. We feel the guidelines are rather conservative and we think it desirable and prudent to be conservative in our approach to recombinant DNA research.

Protection of Proprietary Information

Questions exist under both the NIH guidelines and under several bills pending before the Congress regarding the confidentiality of information available to the government in compliance with inspection and reporting requirements for recombinant DNA research.

We recommend that any measure enacted by the Congress contain provisions protecting proprietary information. Such protection is essential to developmental programs and facilities to bring to the market the benefits of recombinant DNA technology.

Universities and private industry rely on the incentives afforded by the patent system to make the results of their research available to the public.

DNA techniques in insulin biosynthesis. A detailed summary of these proceedings was later submitted to and published by the Nucleic Acid Recombinant Scientific Memorandum, a bulletin distributed by NIH to recombinant DNA scientists.

It is rather obvious that the company has not made any secret of its interest in this significant new field of biological research.

Industrial Research and Safety Considerations

Industrial pharmaceutical research personnel have worked for many years with toxic materials, viruses, and pathogenic bacteria. Scientists have been able to successfully and safely conduct research with these materials because they have the requisite technical training, they follow safety procedures, and they have the appropriate laboratory facilities for such work. Industrial medical research organizations are better equipped and trained than most laboratories to work with the organisms involved in recombinant DNA technology. Such work should involve no greater risks than those currently encountered in biomedical research. We recognize that there has been substantial controversy regarding this aspect of recombinant DNA research. However, we offer the following observations concerning this activity:

(1) The organism used in recombinant DNA research -- that is, E. coli -- has been the major organism for genetic research throughout the world, and no evidence of pathological problems have developed as a result of its widespread use. Further, it and other organisms

research and safety programs; and the need for protection of proprietary information developed in academic institutions and in industry. We will also provide comments on certain aspects of the legislation now pending in the Congress to regulate recombinant DNA research.

Lilly Recombinant DNA Research

Personnel in the Lilly Research Laboratories are engaged in an exploratory effort in which several scientists are looking at potential applications for recombinant DNA technology. This work involves two principal lines of inquiry.

Our scientists are attempting to use recombinant techniques with antibiotic producing microorganisms. Through these procedures, we might create modified organisms that can either synthesize new and better antibiotics or produce an existing antibiotic more efficiently. Although recombinant DNA technology is relatively new, Lilly and many other laboratories have been modifying organisms associated with fermentation procedures by chemical and physical techniques for a number of years.

It is also possible that DNA recombinations may produce hormones and other medically useful proteins. The biosynthesis of insulin is one possibility. In some instances, we may be able to produce significant quantities of materials as a contingency measure to prevent future shortages. In other instances, we may obtain therapeutic agents which are commercially nonexistent today.

STATEMENT

OF

ELI LILLY AND COMPANY

REGARDING RECOMBINANT DNA RESEARCH

TO THE

SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY

OF THE

COMMITTEE ON SCIENCE AND TECHNOLOGY

OF THE

HOUSE OF REPRESENTATIVES

Presented by:

Irving S. Johnson, Ph.D.
Vice President of Research
Lilly Research Laboratories

Thursday, April 28, 1977

(6) Adherence to the guidelines should result in safe procedures. We feel the guidelines are rather conservative in terms of assessed danger, and we think it desirable and prudent to be conservative in our approach to recombinant DNA research.

I would like now to make a brief comment on the protection of proprietary information.

Questions exist under both the NIH guidelines and under several bills pending before the Congress regarding the confidentiality of information available to the Government in compliance with inspection and reporting requirements for recombinant DNA research.

We recommend that any measure enacted by the Congress contain provisions protecting proprietary information. Such protection is essential to developmental programs and facilities to bring to the market the benefits of recombinant DNA technology.

Universities and private industry rely on the incentives afforded by the patent system to make the results of their research available to the public.

The possibility of premature disclosure of research programs and accomplishments with a possible loss of patent rights in the United States and abroad will discourage industrial commitment to the new recombinant DNA technology.

In an organization such as our laboratories, incentives are important to encourage participation in research programs at that point in time when new technology develops.

For example, Lilly's early involvement in tissue culture allowed us to participate at an early stage in the development of poliomyelitis vaccine.

Other examples could be cited such as our activity in the development of anti-tumor agents. We had a somewhat broader program and a different approach than the program that was advocated at that time by the National Cancer Institute and it allowed us to detect and eventually to market drugs that would not have been detected under the NCI program.

We trust that the Congress will carefully evaluate the need for confidential treatment of proprietary information resulting from private research activity. We might note that the interagency task force that Dr. Adams previously referred to, considering recombinant DNA legislation also recommended that proprietary data be protected.

I would like now to make a few brief comments on pending Federal legislation.

As noted earlier in this statement, Lilly supports the enactment of a Federal statute in this field. We feel such an act should place the regulation of recombinant DNA research under the Department of Health, Education, and Welfare. The act should provide for licensure of all facilities engaged in recombinant DNA research with appropriate authority for exemptions from licensure requirements for those activities that do not involve public health or environmental hazards. Consistent with the interagency task force recommendations, we feel research projects should be registered on a confidential basis. We do not feel they should be subject to prior approval.

The legislation should further provide for the issuance of regulations. These initially would be the NIH guidelines with necessary amendments including provisions for the institutional or facility bio-

proceeding and this was accompanied by interviews on our interest while the cameras were filming.

I also participated in the recent public discussions conducted by the National Academy of Sciences on recombinant DNA technology.

I might also note that in May of 1976, Lilly convened an international symposium on the possibility of utilizing recombinant DNA techniques in insulin biosynthesis.

At that time by letter I invited the editor of the AAAS publication, *Science*, to assign a reporter to cover this meeting and report the conference. He did not do so.

A detailed summary of these proceedings was later submitted to and published by the Nucleic Acid Recombinant Scientific Memorandum, a bulletin distributed by NIH to recombinant DNA scientists.

It is rather obvious that the company has not made any secret of its interest in this significant new field of biological research.

I would like now to comment on the nature of industrial research and some of the safety considerations. I might comment that we have established a recombinant biohazard committee with broad representation. While it is in place, industrial pharmaceutical research personnel have worked for many years with toxic materials, oncogenic viruses and pathogenic bacteria. Scientists have been able to successfully and safely conduct research with these materials because they have the requisite training, they follow safety procedures, and they have the appropriate laboratory facilities for such work. Industrial medical research organizations are better equipped and trained than most laboratories to work with the organisms involved in recombinant DNA technology. Such work should involve in my view no greater risks than those currently encountered in biomedical research.

That is a view which I think is shared by Dr. Rene Dubos.

We recognize that there has been substantial controversy regarding this aspect of recombinant DNA research. However, we offer the following observations concerning this activity:

(1) The primary organism used in recombinant DNA research—that is, E coli—has been the major organism for genetic research throughout the world for many years and no evidence of pathological problems have developed as a result of its widespread use. Further, it and other organisms pathogenic for man have been used in the fermentation of therapeutic agents on a production scale—as for example, pseudomonas.

In my discussion at the National Academy of Sciences I described some characteristics of E. coli strains which produced, L-asparaginase——

Mr. THORNTON. I did not understand the word that you used.

Dr. JOHNSON. L-Asparaginase. It is an enzyme which is produced by E. coli, but not a modified E. coli, which is used in the treatment of malignant diseases.

Mr. THORNTON. Thank you, Dr. Johnson.

Dr. JOHNSON. In the example I gave at the forum, I showed some studies that we had made of four strains of E. coli. One was a clinical isolate which had been associated with human disease and the other strains were selected for their ability to produce L-asparaginase, the enzyme which I mentioned.

secretary and general counsel of the company's pharmaceutical division.

Mr. Chairman, as a scientist I would like to commend you and the members of this committee for the very careful and thoughtful manner in which you are approaching the subject of recombinant DNA. We feel that the Congress should consider the imposition of controls on this area of research with great care. Excessive Government controls can have a detrimental effect on innovation and the development of new knowledge and its dissemination. Well intentioned legislation and regulations may give rise to situations comparable to some of our current controversies such as our concerns over artificial sweeteners.

Freedom of scientific inquiry is very precious and efforts to limit the pursuit of new knowledge can be very harmful.

In establishing specific statutory requirements for recombinant DNA research, responsible and reasonable concern for protection of the public health and the environment must be balanced against the possible benefits to human health and nutrition derived from this new technology.

Lilly has been engaged in the research, development, distribution, and production of pharmaceutical products for many years and of agricultural and cosmetic products for a number of years.

The company has a strong commitment to research and has at present in excess of 2,600 scientists and technicians involved in its research programs.

Their activities have made possible a wide variety of products which have benefited both human health and agriculture.

Lilly supports the enactment of legislation to provide appropriate public health and environmental safeguards for recombinant DNA research. In this regard, Lilly endorses the views of the Pharmaceutical Manufacturers Association as expressed by Dr. Adams and Mr. Brennan in the Association's testimony today.

Our purpose in appearing is not to provide a commentary on recombinant DNA research technology. The committee has had excellent testimony from Dr. Maxine Singer and others on recombinant techniques. We will comment briefly on Lilly activities in the recombinant DNA research field; the nature of industrial research and safety programs; and the need for protection of proprietary information developed in academic institutions and in industry. We will also provide comments on certain aspects of the legislation now pending in the Congress to regulate recombinant DNA research.

I would now like to comment briefly on our own efforts in this area.

Personnel in the Lilly Research Laboratories are engaged in an exploratory effort in which several scientists are looking at potential applications for recombinant DNA technology. This work involves two principal lines of inquiry.

Our scientists are attempting to use recombinant techniques with antibiotic-producing micro-organisms. Through these procedures, we might create modified organisms that can either synthesize new and better antibiotics or produce an existing antibiotic more efficiently. Although recombinant DNA technology is relatively new, Lilly and many other laboratories have been modifying organisms associated with fermentation procedures by chemical and physical techniques for a number of years.

Mr. DORNAN. But it was a new Government regulatory list that it was going on?

Dr. ADAMS. Right.

Mr. DORNAN. I could only concur with his statement that night. I thought to myself, it is about time.

Dr. ADAMS. It is a scheduled drug. Because there probably has been some abuse of it.

Mr. DORNAN. Thank you.

Mr. BROWN [presiding]. Gentlemen. I hope that you understand that there is a connection as Mr. Dornan indicated between the question of regulating recombinant DNA and the general attitude about the drug industry. If you lose the support of people like Mr. Dornan in this area, you may be in real trouble.

Mr. BRENNAN. We do not have any information that we will have a loss of that kind of support, Congressman, we think we can make a good record on the questions he is talking about.

Mr. BROWN. I am sure you can.

I am sure it will be of benefit to other Members of the Congress, also.

Gentlemen, I think this is all that we have right at the moment. We appreciate your cooperation, and hope that we can continue to communicate with you on these matters, and hope that this will aid the Congress in coming up with some rational framework in this field.

Mr. BRENNAN. Thank you.

Dr. ADAMS. Thank you very much, Congressman.

Mr. BROWN. One of the firms which belongs to the Pharamecutical Manufacturers Association is Eli Lilly of Indianapolis. We have Dr. Johnson here, vice president of the Eli Lilly Co., and he is accompanied by Mr. John Holt who is secretary and general counsel of the company's pharmaceutical division.

We welcome you gentlemen. Mr. Thornton and hopefully other members of the committee will return as soon as they have voted. But first let us take a very short recess.

[Recess.]

Mr. THORNTON. The subcommittee will come to order. We are very pleased to have you with us today, Dr. Johnson and Mr. Holt, and we would like to ask at this time that you proceed with your testimony.

[Biographical sketches of Dr. Johnson and Mr. Holt follow:]

DR. IRVING S. JOHNSON

Birth date: June 30, 1925.
Birth place: Grand Junction, Colo.
Marital status: Married.
Children: Four.

Education: Westminster College (Navy V-12), 1943–44; Cornell University (USNR Midshipman School), 1944; Havard University (USN Communications School), 1945; Duke University (Marine Biological Station), (summer), 1951; Washburn Mnnicipal University, 1946–48. Degree: A.B., major: Chemistry, minor: Biology. University of Kansas, 1948–53; Degree: Ph. D. major: Zoology. Minor: Bacteriology. Northwestern University (Institute for Management), 1964 (School of Business).

Professional positions: Washburn Municipal University—Assistant Instructor in anatomy and physiology, 1946–48. University of Kansas—Assistant Instructor in embryology, parasitology, and general zoology, 1948–50 Research Assistant on ONR Project No. 164–013. Serological Ontogeny of proteins of heart muscle in the chick embryo, 1950–53. Eli Lilly and Company—Bacteriologist (1953–58); Senior Bacteriologist (1958–60); Research Associate (1960–63); Assistant Director (1963–66); Director, Biological Research Division (1966–72); Executive

And that is one of the things that gives me this very liberal reaction toward regulating the hell out of the pharmaceutical business, particularly when they move into something as sensitive and with the inherent dangers of this DNA research. Will you comment on that?

Dr. ADAMS. Congressman Dornan, I do not know where those statistics come from.

Mr. DORNAN. CBS and NBC generally kick them around.

Dr. ADAMS. I know they have been kicked around. But it seems to me that it is rather difficult to make a flatout statement that three times as many drugs as are needed are made by the pharmaceutical industry. Prescription drugs are prescribed by physicians, so whatever drugs are used in the practice of medicine, as a matter of fact, are being prescribed by them.

Mr. DORNAN. Let me clarify that. That statement meant that some of the major firms were shipping drugs to Mexico to store in large warehouses, and then this came back in as illegal drug traffic. I think we all know that the biggest illegal traffic is operated out of the family medicine chest by young people and others. There are people sharing their pills and prescriptions without the benefit of what the doctor might give them. They are sharing medicine, I know. I think this is probably the biggest area, although undoubtedly some of this may be exaggeration. But is there some sort of trafficking in the overproduction of pills that do not go necessarily through the legal route of a corner pharmacy and a doctor's ball point?

Dr. ADAMS. I think the example you are referring to was the entry of those drugs into an illegal channel of distribution into the United States.

Mr. DORNAN. Yes.

Dr. ADAMS. It was not because the drug was overproduced, it just wound up with the wrong people who then were moving it illegally into the United States.

Mr. BRENNAN. Congressman, let me offer a comment in this area. I think you referred to drugs generally and then drugs with a potential for abuse. On both questions, the U.S. Government over the period of the last decade has had any number of hearings and enacted, we think, a pretty sound law in 1970, the Controlled Substances Act. The World Health Organization and the appropriate U.N. committee, the U.N. Committee on Narcotics has discussed this matter both politically and scientifically over the same period and has determined that there are certain substances subject to abuse, and put a very rational control on them. And in the situation where there is the greatest potential for abuse, and evidence of abuse, it actually established quotas for production.

But they have steadfastly avoided—and these are not just scientists but also politicians—putting controls on the substances, that is, putting quotas on the substances we have a less potential for abuse. And they determined to do that because they felt that there was not any real documentation of the kind of overproduction and overprescribing that you are talking about. There may be some. It is hard to judge whether a doctor is overprescribing, an individual doctor. But on the basis of the evidence, either in the United States or the appropriate world health organizations I would not go that far.

insurance problems that it would create, it could discourage a company from getting into the field at all.

Mr. BROWN. Wouldn't this be true of some of your current research, if you had known what the liabilities were?

For example, we had the thalidomide problem. That involved a very large settlement. And I do not know that anybody could be held to be criminally liable, but they were civilly liable in that situation. That may be a very mild example of what can happen under these circumstances in DNA research.

Mr. BRENNAN. We are not suggesting some statute to limit the liability, it is just that the statutes that we are talking about in our testimony expand the liability for DNA research, they essentially say that if there is an injury, that the person owning the research laboratory, in our case the industry, would be strictly liable. There would be no chance of proving whether there was negligence or lack of due care, they are expanding the normal liability. We are ready to accept the normal liability for what we do in our research laboratory or any other project.

We feel that the companies that insure us understand what that liability is and can relate to it in fixing premiums. If we expand the liability to some strict liability concept, we are afraid we will run into what we did in swine flu, and the insurance companies will say to us, we will not insure you, and that is what the problem is there. We were ready to go ahead and were actually producing hundreds of millions of doses of product while we were waiting for some resolution of the liability problem. Our insurance companies had told us, we are sorry, but we are cutting you off on that.

Mr. BROWN. I am not an expert in matters of liability any more than I am in most other things. But could you just very briefly tell me what the difference is between the term "strict liability," that you used and normal liability?

Mr. BRENNAN. Since I cannot do it rather briefly, Congressman, I will tell you that it is much broader. It eliminates a large area of proof and a large area of consideration by a jury. In the normal case the jury is given a set of facts and can then determine whether, in our case, the manufacturer has violated the standard of care that is necessary for his activity. If he has lived up to that standard of care, then there would be a "not guilty" finding, or no award of damages.

In the strict liability situation, you do not get a chance to argue or discourse about that standard of care, if there is an injury, then liability follows immediately.

Mr. BROWN. Is there an element of liability in the swine flu vaccine situation?

Mr. BRENNAN. Partially, but not entirely. In the swine flu situation it was the universe, the potential universe of injury, or lawsuit, I think really for the insurance company. The expansion of the thing was so enormous and they were quite worried, as I recall it.

There was testimony in the lawsuit that if 200 people were given shots, the day after a certain number of people who got those shots were going to wake up with a fever and probably blame it on the swine flu shots, and a claim would be made and the insurance company would be unable to assess it. I think that was a little different but the

Dr. ADAMS. It has never been a distinct question but I do not think there would be any problem in the appointment of nonscientists or members of the community on institutional biohazards committees.

Mr. HOLLENBECK. To take that one step further, we have heard varying suggestions and varying proposals for the potential makeup of any Government-created regulatory body to deal with DNA.

And we had proposals that have gone to the extent of suggesting that the overseeing committee or body be made up entirely of members of the lay public, labor unions and so on, with the only scientific representation from that part of the scientific community not engaged in DNA research.

I wonder if you could comment on that in particular, and on the whole concept of public participation on a regulatory body generally.

Dr. ADAMS. As a scientist, I would object to that procedure. I think the input from the expert is necessary. I feel that there should be representation of nonscientists as we have indicated in our testimony, representatives of the legal profession, bioethics and others, and lay members of the community, who are necessarily professionals. But I do think to make the wisest possible decision that there must be expertise on that committee from the scientific community, and I think expertise in the field of recombinant DNA. It seems to me that that is really the democratic way to pursue the question.

Mr. HOLLENBECK. Now, you mentioned in your statement that the industry has had some long experience in handling biohazardous materials and that your safety record is ample. What type of records, what kind of checks does industry maintain to ascertain whether there is a good safety record?

How can we be sure that that is the case?

Dr. ADAMS. Let me say that there has never been a major spill of a live virus in production of vaccine. I am certain that there would be some record of an unusual number of cases.

Mr. HOLLENBECK. I am talking about smaller instances—maybe an accidental release or something of that nature.

Dr. ADAMS. The point I am making, Congressman, is that if there had been a spill in a community where a plant is located, there would have been an unusual incidence of, let us say, poliomyelitis or influenza, as the case may be.

That has never been reported and I am certain that our firm would be aware of this. By virtue of precautions that they take in this kind of activity, whether it is research or production, it is very unlikely that these live viruses or bacteria would escape from the plant.

For example, I mentioned in our testimony that our people are rather sophisticated in the field of safety precautions. Many of them use P–3 facilities right now, glove box operations and are rather close to fulfilling the requirements in some cases for a P–4 facility. Now, they don't meet the requirement now, but they are close to it in their P–3 activities.

Mr. HOLLENBECK. I do not want to infringe on the next witnesses' time so I will stop here and ask them the same questions later to get at their particular experiences.

Mr. THORNTON. Mr. Brown.

Mr. BROWN. If I might just raise a couple of questions. I want to compliment you on your statement, Dr. Adams. I think it is a very clear and rational presentation.

ciation would make changes from time to time as additional study and reflection on issues occur. Did you feel that there was a mischaracterization of some change or something?

Dr. ADAMS. Yes, sir, there was a serious misinterpretation that occurred at the meeting called by Dr. Betsy Anker Johnson of the Department of Commerce. We had made our statement on voluntary compliance before Senator Kennedy's committee earlier, and in the meeting with Dr. Betsy Anker Johnson I repeated it. But in an article which appeared in the Washington Post it was made to appear that we had changed our position when in fact we had not. I do not know whether it was a semantic problem or not, but it did lead to a very large number of inquiries directed to my office or elsewhere about whether or not we had changed our position.

We stated earlier that we thought some changes were needed in the NIH guidelines, and we still maintain in our testimony before your committee that these would not affect the safety provisions of the guidelines but were primarily concerned with the administrative features of the guidelines.

That was changed from minor modifications to important changes—and that is a big difference. So that we felt that our position was being misinterpreted. And I know that the subject came up at hearings before this committee and I understand that the record was straightened out on that issue by Dr. Cape and also by Dr. Gartland.

Mr. THRONTON. I noted one possible change in position which is not major, but on which it might be useful to get a clarification.

Mr. Joseph Stetler, testifying before the Subcommittee on Health and Environment on March 18, stated:

> Our principal objections to H.R. 4759 relate to the licensure requirements and restrictions on P–4 facilities. The bill would require that every project involving recombinant DNA Research be licensed under regulations to be promulgated by the Secretary of HEW, subject to review by the advisory committee.
>
> Furtber, the bill would require that all P–4 research and possibly P–3 type research be confined to one of 10 centers to be designated by the Secretary.

In your statement today you said: "We support licensing and inspection of facilities, registration of research projects and mandatory submission of reports."

I think it might be useful to clarify the ground here.

Dr. ADAMS. I would be glad to, Congressman Thornton.

In our testimony before Congressman Rogers, we objected to the licensing of projects. We endorse the concept of the licensing facilities. We also endorse the registration of the project but not the licensing.

So that our objection in the testimony before Congressman Rogers was to a licensing of individual projects but we have always endorsed the concept of registering those projects.

Mr. BRENNAN. Congressman, the reason for that is that a licensing authority is obviously a preclearance. And if the Federal Government or any other Government agency is licensing the project, it essentially means that the head of NIH or the Secretary of HEW is just directing all the research in the country.

Mr. THORNTON. Mr. Hollenbeck.

Mr. HOLLENBECK. Thank you, Mr. Chairman.

Can you speculate when industry may be ready to move into production-level operations?

Mr. BRENNAN. Congressman, if I can add something, I think there is a great deal of current concern in a number of localities across the country because no one seems to have yet come to grips with regulating this subject. I think if the Federal Government does enact legislation which would establish the kind of standards that are appropriate, that a good deal of that concern would be diminished and and I think that likewise our concern with local regulation would be diminished.

Dr. ADAMS. Congressman Thornton, I think that once Federal legislation is passed and the public is assured that safety problems have been very thoroughly considered by scientists, academic scientists and industry scientists and by people who are expert in the field of bioethics, there would be the assurance that is needed and I think the clamor for local options would pretty much be dissipated.

But until that legislation exists, I think people are concerned about voluntary compliance with guidelines.

Now, we have indicated, as outlined in our testimony, that we are committed to voluntary compliance with those guidelines. But I do not think the public is willing to accept them. I think they are going to be much more reassured when there is legislation on the books that will impose Government standards, the violation of which obviously would present rather serious consequences.

Mr. THORNTON. I think what I am trying to get at is not to question whether it would have these consequences, because I do understand your position with regard to preemption. You do not think that State and local governments should have the authority to promulgate, on their own, higher or stricter standards than those which are nationally acceptable, assuming that national standards are made effective. I understand that.

Dr. ADAMS. Let me state it this way, I would have no objection. I think a community should have some voice. I would hope that they would not have to impose more rigid standards, that the standards as they are finally promulgated at the Federal level will be adequate. I do not think there is any way in which that can be overcome.

Mr. BRENNAN. I think that what we suggest, Congressman, and it has been outlined in some of the pending legislation—is that there be a screening by the Secretary of HEW or the designated health authority of requests for regulation of a more stringent nature, and that there be some flexibility in that Federal official, that is, that we may or may not grant the local authority the opportunity to impose a stricter regulation, rather than be required to do so.

Mr. THORNTON. In order that I may understand the suggestion, which is what I am really seeking to understand, I'll give you a hypothetical situation to try to arrive at it. What if a community north of San Francisco were to pass an ordinance prohibiting the construction of a high containment facility at or near the San Andreas fault, out of some concern, whether real or imaginary, that they might be subject to physical damage in that area? Under the mechanism which you are referring to, that action would be referred to an appeals decision at the Federal regulatory level, whereupon a determination would be made whether such a waiver or additional restriction was reasonable and should be approved or granted. Is that what you are suggesting?

Westwood Pharmaceuticals Inc.
468 Dewitt Street
Buffalo, New York 14213
(716) 882-8484

Winthrop Laboratories
Div. of Sterling Drug Inc.
90 Park Avenue
New York, New York 10016
(212) 972-4141

Wyeth Laboratories
Div. of American Home Products Corp.
P.O. Box 8299
Philadelphia, Pennsylvania 19101
(215) 688-4400

The Zemmer Company
231 Hulton Road
Oakmont, Pennsylvania 15139
(412) 361-2728

Zimmer-USA, Inc.
727 North Detroit Street
Warsaw, Indiana 46580
(219) 267-6131

Mead Johnson & Company
2404 Pennsylvania Street
Evansville, Indiana 47721
(812) 426-6000

Merck & Co., Inc.
126 East Lincoln Avenue
Rahway, New Jersey 07065
(201) 381-5000

Merck Chemical Division
Merck & Co., Inc.
126 East Lincoln Avenue
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Merck Sharp & Dohme
Div. of Merck & Co., Inc.
West Point, Pennsylvania 19486
(215) 699-5311

Merrell-National Laboratories
Div. of Richardson-Merrell Inc.
110 East Amity Road
Cincinnati, Ohio 45215
(513) 821-3811

Morton-Norwich Products, Inc.
110 North Wacker Drive
Chicago, Illinois 60606
(312) 621-5795

Organon Inc.
375 Mt. Pleasant Avenue
West Orange, New Jersey 07052
(201) 731-6000

Ortho Diagnostics Inc.
U.S. Highway 202
Raritan, New Jersey 08869
(201) 524-2121

Ortho Pharmaceutical Corporation
U.S. Highway 202
Raritan, New Jersey 08869
(201) 524-0400

Parke, Davis & Company
Box 118, G.P.O.
Detroit, Michigan 48232
(313) 567-5300

S.B. Penick & Company
A Unit of CPC International Inc.
1050 Wall Street West
Lyndhurst, New Jersey 07071
(201) 835-6600

Pennwalt Prescription Products
Pharmaceutical Div., Pennwalt Corp.
P.O. Box 1710
Rochester, New York 14603
(716) 271-1000

Pfizer Inc.
235 East 42nd Street
New York, New York 10017
(212) 573-2323

Pharmacia Laboratories Inc.
800 Centennial Avenue
Piscataway, New Jersey 08854
(201) 469-1222

Philips Roxane Laboratories, Inc.
330 Oak Street
Columbus, Ohio 43216
(614) 228-5403

Wm. P. Poythress & Co., Inc.
P.O. Box 26946
Richmond, Virginia 23227
(804) 644-8591

The Purdue Frederick Company
50 Washington Street
Norwalk, Connecticut 06856
(203) 853-0123

Reed & Carnrick
30 Boright Avenue
Kenilworth, New Jersey 07033
(201) 272-6600

Rexall Drug Company
3901 North Kingshighway Blvd.
St. Louis, Missouri 63115
(314) 383-1234

Riker Laboratories, Inc.
19901 Nordhoff Street
Northridge, California 91324
(213) 341-1300

A.H. Robins Company
1407 Cummings Drive
Richmond, Virginia 23220
(804) 257-2000

William H. Rorer, Inc.
500 Virginia Drive
Fort Washington, Pennsylvania 19034
(215) 628-6000

Ross Laboratories
Div. of Abbott Laboratories
825 Cleveland Avenue
Columbus, Ohio 43216
(614) 228-5281

Bristol-Myers Company
345 Park Avenue
New York, New York 10022
(212) 644-2100

Bristol Laboratories
Div. of Bristol-Myers Company
P.O. Box 657
Syracuse, New York 13201
(315) 470-2000

Bristol-Myers Products
Div. of Bristol-Myers Company
345 Park Avenue
New York, New York 10022
(212) 644-2100

Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, N.C. 27709
(919) 549-8371

The Central Pharmacal Company
112-128 East Third Street
Seymour, Indiana 47274
(812) 522-3915

Ciba-Geigy Corporation
Pharmaceuticals Division
556 Morris Avenue
Summit, New Jersey 07901
(201) 277-5000

Cole Pharmacal Company, Inc.
P.O. Box 14404
St. Louis, Missouri 63178
(314) 534-7500

Commercial Solvents Corporation
245 Park Avenue
New York, New York 10017
(212) 661-5454

Cooper Laboratories, Inc.
1259 Route 46
Parsippany, New Jersey 07054
(201) 334-9800

Cutter Laboratories, Inc.
4th & Parker Streets
Berkeley, California 94710
(415) 841-0123

Difco Laboratories
P.O. Box 1058-A
Detroit, Michigan 48232
(313) 961-0800

Dome Laboratories
Div. Miles Laboratories, Inc.
400 Morgan Lane
West Haven, Connecticut 06516
(203) 934-9225

Dorsey Laboratories
P.O. Box 83288
Lincoln, Nebraska 68501
(402) 464-6311

The Dow Chemical Company
Indianapolis Division
P.O. Box 68511
Indianapolis, Indiana 46268
(317) 873-5311

E.I. duPont deNemours & Company
Pharmaceuticals Div., Biochemicals Department
1007 Market Street
Wilmington, Delaware 19898
(302) 774-5065

Eaton Laboratories
Div. of Morton-Norwich Products,Inc.
17 Eaton Avenue
Norwich, New York 13815
(607) 335-2111

Endo Laboratories, Inc.
1000 Stewart Avenue
Garden City, New York 11530
(516) 832-2210

Ethicon, Inc.
Route 22
Somerville, New Jersey 08876
(201) 524-0400

Ferndale Laboratories, Inc.
780 West Eight Mile Road
Ferndale, Michigan 48220
(313) 548-0900

First Texas Pharmaceuticals, Inc.
P.O. Drawer 44079
Dallas, Texas 75234
(214) 243-4371

C.B. Fleet Co., Inc.
4615 Murray Place
Lynchburg, Virginia 24505
(804) 845-2375

5. Information in our files does not indicate the level of risk associated with the research in which our member firms are engaged. It is fair to assume, however, that such research is being conducted in compliance with the NIH Guidelines.

Please let us know if we can be of further assistance.

Sincerely yours,

John G. Adams

JGA:ga

Enc.

from constructing their own P–4 facilities. Once the Congress establishes the ground rules for this type of research, they should be applied equally to all qualified parties. Designating approved centers and limiting their numbers would amount to the creation of a Federal monopoly on recombinant DNA research.

Two of the pending bills, H.R. 4232 and S. 945, provide for the establishment of a new commission to study and evaluate recombinant DNA research and technology. We agree that there will be a need to review progress in this field periodically, in order to provide adequate safeguards for the public and for the environment; but expert committees already in place are performing this function, including the NIH Advisory Committee, the Interagency Committee and the National Commission for the Protection of Human Subjects.

We would not object to the creation of a separate commission, but consideration should be given to the use of existing commissions or committees for this purpose. We would endorse wider representation of nonscientists on such advisory groups if, in fact, there is inadequate representation of such persons at present.

And finally, the provisions of section 11 of S. 1217 concerning employee discrimination are excessive in our opinion. This proposed system for handling cases of employee/employer discrimination complaints seems to be unnecessary. Currently, there is a related but less punitive procedure available under section 11(c) of the Occupational Safety and Health Act of 1970 (29 U.S.C. section 669(c)). We recommend that any provision in recombinant DNA legislation intended to proscribe reprisals against employees be consistent with those provisions.

There are other provisions of pending legislation that will require amendment in order for the Congress to enact the best possible legislation in this field. We have exerted considerable effort to assist in that process and will continue to do so. Government, industry, academia, and the public have a responsibility to fully examine all of the issues involving recombinant DNA research in order to construct legislation that will protect the public and environment, dispel baseless anxiety and emotion and encourage important basic research. We are pledged to continue our efforts to facilitate that process.

This concludes our prepared statement, Mr. Chairman. Mr. Brennan and I will be pleased to respond to your questions.

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

I appreciate your testimony.

Could you provide for us a list of the 129 firms that are members of the association, just for our record.

Dr. ADAMS. I will be pleased to.

[The material referred to above follows:]

Dr. ADAMS. We have stated in every hearing or meeting in which we have participated that member firms of the PMA will voluntarily comply with the NIH guidelines. Since the guidelines were written primarily, if not exclusively, for research sponsored by the National Institutes of Health, some clarification of their application to industrial or other non-NIH-sponsored research is needed. I would like to emphasize as strongly as I can at this time that the necessary modifications will in no way compromise the biological or physical containment provisions of the guidelines. These provisions are the operative part of the guidelines and we have not, and will not suggest any change in them. Our concerns relate to administrative features of the guidelines that in our view can be readily and safely modified to assure their applicability to non-NIH-sponsored recombinant DNA research. It is of interest to note that the Interagency Committee recognized the need for modification and its March 15 report recommended one of the major changes we suggested.

In our public statements, we have pointed to the need for some provision in the guidelines to protect the confidentiality of information submitted to the Government in compliance with the requirements for inspection and reporting.

In our testimony and comments on proposed legislation we have suggested that such protection be incorporated into any bill that may ultimately be enacted. Amendatory language to accomplish this purpose has been submitted to the Health Subcommittees of both Houses of Congress and is attached to this testimony as an appendix.

In effect, the amendment would provide such protection under the exemption provisions of the Freedom of Information Act, and would be reinforced by the provisions of the Non-Nuclear Energy Research Act of 1975. This safeguard for industrial property rights was recognized as a necessary incentive for research in the report of the President's Biomedical Research Panel and in the report of the Interagency Committee on Recombinant DNA Research.

A very minor point in our earlier testimony concerned the restriction in volume of cultures containing recombinant DNA molecules. We pointed out that in any commercial scaleup, if indeed commercial development ever becomes a reality, 10 liters would probably not be adequate for purposes of developmental pilot plant operations. The point is somewhat academic at this time, but it is a consideration which will be necessary with advancing technology. I hasten to add that compliance with other provisions in the guidelines, for example, the biological and physical containment requirements would preclude the commercial development of any recombinant DNA material that would pose a threat to the public health or environment. We are confident that clarification on this point will be forthcoming in pending legislation and the regulations promulgated thereunder. In the meantime, our member firms are committed to voluntary compliance with the guidelines.

As I am sure you are aware, PMA advocates legislation and regulation in this field of research. We have cooperated with officials at NIH and other Government agencies, including Members of Congress, in seeking the statutory and regulatory controls which we and they deem to be necessary.

VI. LICENSE REVOCATION

SEC. 475. (a) If the Secretary finds, after reasonable notice and opportunity for a hearing to a person licensed under this part to conduct recombinant DNA research, that such person --

(1) has been guilty of misrepresentation in obtaining such license,

(2) has failed to comply with the terms and conditions upon which such license was issued or renewed, or

(3) has failed or refused to permit an inspection authorized by section 474,

the Secretary may revoke the license of such person for the remainder of its term or may make such person ineligible to apply for a license under this part for such period as the Secretary may prescribe, or may take both such actions.

V. INSPECTIONS

SEC. 474. (a) For the purposes of enforcement of the licensing requirements of this part, officers, employees, or agents designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator or agent in charge, are authorized to enter and inspect at reasonable times, in a reasonable manner and within reasonable limits any establishment licensed under Section 472 or in which recombinant DNA is present or is being produced. Such an inspection may extend only to pertinent records, files, papers, facilities, equipment and other items in the establishment that are directly related to such license, possession or production to determine:

(1) whether the establishment conforms to the requirements for obtianing or holding a license under section 472; and

(2) whether the establishment conforms to any applicable standards established pursuant section 471.

(b) Upon completion of any such inspection and prior to leaving the premises, the officer, employee, or agent making the inspection shall give to the owner, operator, or agent in charge a prelimimary report which summarizes any conditions or practices observed by him which, in his judgment, indicate a violation of the licensing requirements of this part. He shall also prepare a written final report of his findings and send it to such owner,

III. LICENSES

SEC. 472. (a) Effective one hundred and eighty days after the date of the enactment of this part, any person who owns or operates an establishment which engages in recombinant DNA research must hold a license issued under this part authorizing such person to engage in such research.

(b) A license to authorize a person to engage in recombinant DNA research shall be issued only upon an application made by such person in such form and manner as may be prescribed by the Secretary. An application for such a license shall include an agreement that the applicant will comply with the standards promulgated under section 471 and such additional information as the Secretary may provide.

II. STANDARDS

PART I -- REGULATION OF RECOMBINANT DNA RESEARCH

DEVELOPMENT OF STANDARDS

SEC. 471. (a) Within one hundred and eighty days of the date of enactment of this part, the Secretary shall promulgate as standards regulations to:

(1) prescribe physical and biological containment requirements for recombinant DNA research.

(2) prescribe requirements respecting laboratory safety techniques to be followed by personnel involved in recombinant DNA research.

(3) prescribe requirements respecting the establishment and operation of institutional review committees for recombinant DNA research projects.

(4) prescribe requirements establishing safeguards for the transportation of host/vector systems containing recombinant DNA.

(5) prescribe requirements respecting reports to be made by persons engaged in recombinant DNA research; and

(6) include such other provisions as the Secretary determines to be necessary for the effective administration of the requirements of this part.

We realize that our suggestions may raise questions from members of the Subcommittee as well as the staff. We would welcome the opportunity to further discuss our suggestions at any time.

There are other portions of H.R. 4759 which we alluded to during our testimony, such as the section on "Designation of Centers", but on which we are not submitting amendatory language. In those circumstances, we felt that we were not able to offer constructive assistance to the Subcommittee beyond our testimony. Please understand that this does not in any way alter the positions which we expressed during the course of our testimony on March 17.

We hope that our recommendations will be useful to you and the members of the Subcommittee and that we will have an opportunity to continue to work with you on this most important subject.

Sincerely,

C. Joseph Stetler

Enclosures

bcc: Messrs. Adams, Brennan, Steve Lawton

RELEASE OF PROPRIETARY INFORMATION

Add the following as a new Section:

"Any information reported to or otherwise obtained by the Secretary or his representative pursuant to this Act which is exempt from disclosure pursuant to section 552 of Title 5, United States Code shall be considered confidential and shall not be disclosed. Upon a showing satisfactory to the Secretary by any person that any information, or portion thereof obtained under this Act by the Secretary or his representative either directly or indirectly from such person, would, if made public, divulge (1) trade secrets or (2) other proprietary information of such person, the Secretary or his representative shall not disclose such information and disclosure thereof shall be punishable under section 1905 of Title 18 U.S.C."

EMPLOYEE PROTECTION

1. Amend Section (b) as follows:

"(b) (1) Any employee who believes that the employee has been discharged or otherwise discriminated against by any person in violation of subsection (a) of this section may, within 30 days after such alleged violation occurs, file (or have any person file on the employee's behalf) a complaint with the Secretary of Labor (hereinafter in this section referred to as the "Secretary") alleging such discharge or discrimination. Upon receipt of such a complaint, the Secretary shall notify the person named in the complaint of the filing of the complaint, and shall conduct an investigation of the violation alleged. If upon such investigation, the Secretary determines that the provisions of this subsection have been violated, he shall bring an action in any appropriate United States district court against such person. In any such action the United States district courts shall have jurisdiction, for cause shown to restrain violations of paragraph (a) of this subsection and order all appropriate relief including rehiring or reinstatement of the employee to his former position with back pay.

(2) Within 90 days of the receipt of a complaint filed under this subsection the Secretary shall notify the complainant of his determination under paragraph 1 of this subsection."

2. Delete current Sections 11 (b) (1) through 11 (e).

his findings and send it to such owner, operator, or agent within thirty days of the completion of the inspection.

(c) No officer, employee, or agent designated by the Secretary to enter an establishment and conduct an inspection pursuant to this section shall be required to obtain a search warrant from any judicial officer prior to entering any establishment and conducting any inspection which is authorized by this section.

REGISTRATION OF RESEARCH PROJECTS

Amend Section 6 as follows:

Any person who is responsible for undertaking a project ~~The Secretary shall register any project involving~~ involving recombinant DNA shall register the project ~~recombinant DNA if the request for registration is~~ with the Secretary and shall provide ~~accompanied~~ by such information as the Secretary may prescribe concerning recombinant DNA activities which are part of that project.

PHARMACEUTICAL MANUFACTURERS

C. JOSEPH STETLER
PRESIDENT

1155 FIFTEENTH STREET, N.W.
WASHINGTON, D.C. 20005
AREA CODE 202 [illegible]

April 13, 1977

The Honorable Edward M. Kennedy
Chairman, Subcommittee on Health
and Scientific Research
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

During the course of our testimony before the Health Subcommittee on April 6 concerning S. 1217, 95th Congress, we suggested a number of amendments. We are enclosing specific amendatory language which would implement our recommendations.

Of particular concern to us is the potential conflict in those portions of the bill relating to licensing of facilities and registration. After hearing the testimony of Secretary Califano and Dr. Frederickson, it was apparent to us that there are some drafting effors in the bill. The testimony of the HEW witnesses made it clear that the intention of the administration was to have the concept of licensing apply only to facilities. Therefore, we have incorporated amendatory language in the attached list of recommendations which would give effect to the principle of the licensing of facilities and the registration of research projects.

We realize that our suggestions may raise questions from members of the Subcommittee as well as your staff. We would welcome the opportunity therefore to further discuss these suggestions at any time.

Sincerely,

C. Joseph Stetler

Enclosures

ESTABLISHMENT OF A FEDERAL ROSTER OF PERSONS AUTHORIZED TO ENGAGE IN SUCH RESEARCH.

4. Breach of Standards - Grounds for Revocation of License

WE AGREE WITH THIS POINT. OUR READING OF SECTION 5 OF THE BILL PROVIDES NECESSARY AUTHORITY.

5. Licensure Contingent on Adequate Safety Standards

WE AGREE.

6. Continuing Study of Ethical, Societal and Legal Implication of DNA Research

WE AGREE.

7. Public Right to Know Who, Where and Under What Conditions

WE AGREE.

8. Funding and Staffing

IMPOSSIBLE TO ESTIMATE WITHOUT ADDITIONAL DETAILS.

9. Limit on Number of Facilities

NO.

10. Environmental Impact Statement

SHOULD BE REQUIRED.

MR. CHAIRMAN, THAT CONCLUDES OUR TESTIMONY. WE WILL BE PLEASED TO SUPPLY THE COMMITTEE WITH SPECIFIC AMENDATORY LANGUAGE COVERING THE SUGGESTIONS WE HAVE MADE. WE WILL ALSO BE PLEASED TO RESPOND TO ANY QUESTIONS WHICH YOU MIGHT HAVE.

WHICH THE INDUSTRY ALREADY HAS IN DEALING WITH THESE AND OTHER SUBSTANCES IN RESEARCH ENDEAVORS, WE FEEL THERE IS NO EVIDENCE TO SUPPORT THIS TYPE OF REQUIREMENT. PERSONS INJURED AS A RESULT OF RECOMBINANT DNA RESEARCH WOULD CLEARLY BE COVERED UNDER EXISTING INSURANCE PROGRAMS. THIS WOULD SEEM TO BE TRUE ALSO IN ACADEMIC INSTITUTIONS. FINALLY, WE QUESTION WHETHER A PROVISION OF THIS SORT SHOULD BE ENACTED IN VIEW OF THE VARIETY OF STATE STATUTES AND DECISIONS WHICH WOULD PROVIDE RELIEF UNDER LIABILITY CIRCUMSTANCES.

S. 945, 95TH CONGRESS

THE RECOMBINANT DNA STANDARDS ACT OF 1977, S. 945, TAKES A SOMEWHAT DIFFERENT APPROACH TOWARD REGULATION. THE BILL WOULD AUTHORIZE THE SECRETARY OF HEW TO PROMULGATE STANDARDS RELATING TO SUCH RESEARCH. IT WOULD ALSO AUTHORIZE HIM TO CONDUCT INSPECTIONS IN ORDER TO DETERMINE WHETHER A RESEARCH FACILITY WAS BEING OPERATED IN COMPLIANCE WITH THE VARIOUS PROVISIONS OF THE ACT. AGAIN, THE ATTORNEY GENERAL, ON A DETERMINATION BY THE SECRETARY THAT A FACILITY'S RECOMBINANT DNA RESEARCH WAS ENDANGERING THE PUBLIC HEALTH, COULD BRING SUIT TO ENJOIN THAT ACTIVITY. THE BILL WOULD ALSO AUTHORIZE INDIVIDUALS TO INITIATE A LAWSUIT FOR AN INJUNCTION ON GROUNDS THAT THE CONTINUATION OF RESEARCH AT A PARTICULAR FACILITY WOULD BE A SIGNIFICANT HAZARD TO THE PUBLIC HEALTH. IF THE CITIZEN SUCCEEDED IN OBTAINING AN INJUNCTION, THE OFFENDING FACILITY WOULD BE ASSESSED ATTORNEY'S FEES, WITNESS FEES, AND OTHER REASONABLE COSTS OF LITIGATION.

WITH RESPECT TO PENALTIES, THE BILL PROVIDES THAT A VIOLATION OF ANY REGULATION PROMULGATED UNDER THE ACT WOULD BE A MISDEMEANOR AND WILLFUL VIOLATIONS WOULD BE CLASSIFIED AS FELONIES.

S. 621, 95TH CONGRESS

S. 621, THE "DNA RESEARCH ACT OF 1977", WOULD AUTHORIZE THE SECRETARY OF HEW TO PROMULGATE GUIDELINES APPLICABLE TO EITHER PUBLIC OR PRIVATE ORGANIZATIONS. THE BILL WOULD ALSO IMPOSE CERTAIN RESTRICTIONS ON PATENTS BY LINKING THE GRANTING OF PATENTS TO ADHERENCE TO THE GUIDELINES, AS WELL AS REQUIRING FULL DISCLOSURE OF INFORMATION WITH RESPECT TO PROCESSES AND ORGANISMS. THE HEW SECRETARY WOULD BE AUTHORIZED TO ISSUE LICENSES FOR RESEARCH AND TO SEEK AN INJUNCTION AGAINST A RESEARCH FACILITY BELIEVED BY THE SECRETARY TO BE A SIGNIFICANT HAZARD TO THE PUBLIC HEALTH. FEDERAL AGENTS COULD CONDUCT INSPECTIONS IN ORDER TO DETERMINE WHETHER RESEARCH FACILITIES WERE BEING OPERATED IN COMPLIANCE WITH THE ACT, THE GUIDELINES, AND THE TERMS OF ANY LICENSE. PERSONS DOING RESEARCH WITH RECOMBINANT DNA WOULD BE HELD STRICTLY LIABLE WITHOUT REGARD TO FAULT FOR ANY INJURY CAUSED BY SUCH RESEARCH.

THE PRINCIPAL REGULATORY TOOL IN THIS BILL IS THE LICENSING SYSTEM. WE BELIEVE ITS TERMS ARE TOO BROAD AND NEED TO BE REDEFINED. FURTHER, WE NOTE THAT THE FEES TO BE CHARGED FOR SUCH LICENSES COULD BE UTILIZED TO ENFORCE THE SECRETARY'S GUIDELINES. IF THAT WERE CONSTRUED TO MEAN PAYING THE SALARIES AND EXPENSES OF INSPECTORS AND THE CENTRAL OFFICE FORCE WHICH WOULD REVIEW ALL OF THE INSPECTION REPORTS, THE RESULTANT HIGH LICENSING FEES COULD, IN EFFECT, BAN USEFUL RESEARCH BY SMALL LABORATORIES.

TWO OTHER PROVISIONS OF THIS BILL WARRANT COMMENT. THE RESTRICTIONS ON PATENTS WHICH THE BILL WOULD ESTABLISH ARE UNNECESSARY AND COULD WORK AS A DISSERVICE TO THE PUBLIC BY DISCOURAGING RESEARCH. WE ARE GENERALLY OPPOSED TO SPECIFIC LIMITATIONS ON THE GENERAL PATENT LAWS, SUCH AS THE ONE IN SECTION 6, WHICH WOULD PRECLUDE THE GRANTING OF A PATENT UNLESS ALL GUIDELINES HAVE BEEN STRICTLY FOLLOWED. WE BELIEVE

IS IN COMPLIANCE WITH FEDERAL STANDARDS AND IS MEETING NECESSARY SAFETY REQUIREMENTS. TO GO BEYOND THAT POINT AND REQUIRE PREAPPROVAL BY THE SECRETARY OF RESEARCH PROJECTS WOULD CREATE SUBSTANTIAL IMPEDIMENTS TO THE CONDUCT OF THE RECOMBINANT DNA RESEARCH. IN EFFECT, IT WOULD PLACE THE SECRETARY IN THE POSITION OF DIRECTING ALL SUCH RESEARCH CONDUCTED WITHIN THE UNITED STATES. AS WE UNDERSTAND THE RECOMMENDATIONS OF THE FEDERAL INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH AND THE TESTIMONY OF DR. FREDERICKSON BEFORE THE HOUSE SUBCOMMITTEE ON SCIENCE, RESEARCH AND TECHNOLOGY ON MARCH 31, THE ADMINISTRATION WOULD ALSO SUPPORT THIS APPROACH.

WE DO NOT FIND ANY SPECIFIC PROVISIONS IN S. 1217 WHICH WOULD PROTECT THE CONFIDENTIALITY OR TRADE SECRET STATUS OF PROPRIETARY INFORMATION SUBMITTED TO THE SECRETARY AS PART OF THE REPORTING PROCESS OR AS PART OF AN APPLICATION FOR LICENSE. THE PHARMACEUTICAL INDUSTRY SUPPORTS THE SUBMISSION OF SUFFICIENT INFORMATION TO THE SECRETARY TO DESCRIBE RESEARCH PROGRAMS WHICH ARE BEING UNDERTAKEN IN THIS CRITICAL AREA. AT THE SAME TIME, IF THAT RESEARCH IS TO BE GIVEN EVENTUAL COMMERCIAL APPLICATION AND IF PRIVATE RESOURCES ARE TO FINANCE THIS RESEARCH, THERE MUST BE SOME PROTECTION GIVEN TO TRADE SECRET DATA. WE WOULD LIKE TO OFFER AN AMENDMENT TO THE BILL WHICH WE BELIEVE WOULD PROVIDE THAT SORT OF PROTECTION AND NOT IMPEDE THE REGULATORY PROCESS OR INTERFERE WITH THE SECRETARY'S UNDERSTANDING OF THE SCOPE OF THE RESEARCH BEING CONDUCTED. OUR AMENDMENT IS MODELED AFTER SIMILAR PROVISIONS IN THE FEDERAL NON-NUCLEAR ENERGY RESEARCH AND DEVELOPMENT ACT.

SECTION 11 OF THE BILL PROPOSES A SYSTEM UNDER WHICH AN EMPLOYEE, WHO WAS DISCHARGED OR FEELS DISCRIMINATED AGAINST BECAUSE OF TESTIMONY OR OTHER ACTIONS TAKEN BY HIM IN A PROCEEDING AGAINST HIS EMPLOYER

SINCE THAT TIME, WE HAVE CONTINUED TO WORK WITH STATE AND FEDERAL LEGISLATIVE AND REGULATORY BODIES AS THEY HAVE WEIGHED THE NEED FOR PUBLIC INVOLVEMENT IN THIS FRONTIER FIELD OF SCIENCE. WE OFFICIALLY COMMENTED TO THE DEPARTMENT OF HEW IN NOVEMBER ON THE NIH GUIDELINES AND REITERATED THE INTENTION OF PMA MEMBER FIRMS TO VOLUNTARILY COMPLY WITH THEM. WE HAVE ALSO SOUGHT FROM NIH A CLARIFICATION OF THE CONFIDENTIALITY OF INFORMATION ASPECTS OF THE GUIDELINES.

EARLY IN MARCH OF THIS YEAR, WE AGAIN SURVEYED PMA MEMBER FIRMS TO DETERMINE THEIR CURRENT INVOLVEMENT IN RECOMBINANT DNA RESEARCH. CONTRARY TO SOME ALLEGATIONS THAT THE DRUG INDUSTRY IS HEAVILY ENGAGED IN SUCH RESEARCH, OUR SURVEY FOUND THAT ONLY THREE PMA FIRMS ARE NOW SO ENGAGED IN THEIR OWN FACILITIES. THREE OTHER FIRMS ARE SPONSORING SUCH RESEARCH THROUGH GRANTS OR CONTRACTS. ADDITIONAL DETAILS OF OUR SURVEY HAVE BEEN PROVIDED TO NIH, AND WE SHALL BE PLEASED TO MAKE THEM AVAILABLE TO THE SUBCOMMITTEE IF YOU WISH.

ALTHOUGH WE ARE CONCERNED ABOUT CERTAIN PROVISIONS OF THE PENDING PROPOSALS, WE AGREE THAT LEGISLATION SHOULD BE ENACTED IN ORDER TO PROVIDE ADEQUATE SAFEGUARDS, ENFORCEMENT MECHANISMS, AND RESEARCH ENCOURAGEMENT. IN ORDER TO SATISFY THESE INTERESTS, UNIFORM NATIONAL STANDARDS SHOULD BE ESTABLISHED FOR ALL RECOMBINANT DNA RESEARCH, WHETHER CONDUCTED UNDER PUBLIC OR PRIVATE AUSPICES. INDIVIDUAL FACILITIES AT WHICH SUCH RESEARCH IS CARRIED ON SHOULD BE REGULATED BY THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE. THE SECRETARY OF HEW SHOULD ALSO BE GIVEN AUTHORITY TO INSPECT THOSE FACILITIES FOR COMPLIANCE WITH SAFETY AND OTHER REQUIREMENTS. WE ALSO FEEL THAT FEDERAL LEGISLATION SHOULD REQUIRE THE ESTABLISHMENT OF INSTITUTIONAL REVIEW COMMITTEES.

passage of legislation will, in our opinion, assure the avoidance of any unreasonable risk to the public, or to the environment. It is for this reason that we foresee no immediate cause for concern or involvement by the Environmental Protection Agency. As experience is gained in the field, or at such time as there are developments that suggest risks greater than are now known or anticipated, there may be need to consider additional controls. In such case, we feel the Interagency Committee, or a similar advisory body, would be an appropriate forum for such consideration and that delegation of additional regulatory authority could be determined at that time.

It is the considered opinion of our experts in the field that the present system of physical and biological containment as required by the Guidelines offer adequate protection of persons and the environment. We are aware of the controversy surrounding the selection and monitoring of the presently available host-vector systems but are satisfied that with appropriate physical containment the risks involved can be minimized or eliminated. We are hopeful that research in the field will result in the development of even more enfeebled host-vector systems but in the meantime, there does not appear to be any undue risk in the appropriate use of EK1 and EK2 systems. There may be a need to establish markers for existing and new strains of host cells or of host-vector systems. Whether there is a need for targeted research in this area is a matter which must be determined by experts in the field. Responsibility for such research is a matter that probably should be referred to an appropriate advisory body. It will only be through such research that the necessity or feasibility of monitoring can be established.

Mr. Chairman, this completes my brief statement. I shall be happy to answer any questions you or members of the Committee may have.

On all of these occasions, we have stated that member firms of our Association engaged in recombinant DNA research would voluntarily comply with the NIH Guidelines. We did request some clarification of the Guidelines relative to the protection of industrial property rights, and to the eventual need for modification of the volume restriction should commercial scale-up become a reality. However, we stated unequivocally our intention to voluntarily comply with the physical and biological containment provisions. We have met with officials of the National Institutes of Health on several occasions in the interest of modifying the Guidelines to recognize the need for protection of confidential information, particularly in the case of industrial firms engaged in such research. We feel that these meetings have been productive and that our concerns were adequately addressed in the Report of the Interagency Committee. Most recently, we have endorsed the need for legislation and regulations promulgated thereunder to provide additional assurances to the public.

I believe it is important for this Committee to be made aware of the present level of involvement by industry. At the request of Dr. Fredrickson, Chairman of the Interagency Committee, we updated an earlier survey of our member firms. Contrary to allegations in the press and in recent Congressional hearings that the drug industry is heavily engaged, our survey showed that only three firms are conducting recombinant DNA research in their own facilities, and that three additional firms are sponsoring academic research in the field. A similar survey was conducted by the Industrial Research Institute and as reported in the Wall Street Journal, three additional non-drug industry firms were involved. Results of both surveys have been submitted to the Chairman of the Interagency Committee.

mittee on Human Resources, and by the Environmental Protection Agency.

In addition, we participated in a meeting of industry representatives and officials of the Department of Commerce in November 1976 and have met with representatives of NIH on several occasions. Our purpose on each of these occasions was to state the position of the association on recombinant DNA research which, contrary to some allegations, has not changed since our first public statement in September 1976. I believe that it is clear on the record that the drug industry has acted cooperatively and responsibly in seeking the best possible solution to this most important public policy issue. Copies of the aforementioned documents are appended to this testimony, and we respectfully request that they be made part of the record of this hearing.

Mr. THORNTON. Without objection, those documents will be included in the record of the hearing.

Dr. ADAMS. They were included in the copies sent to you.

[The documents are as follows:]

The Drug Trademark on Trial -- An Omen for All Consumer Goods: Proceedings, 95th Annual Meeting of the U. S. Trademark Association, San Diego, California (May 21, 1973)

How the Kennedy Drug Bill Could Affect the Physician's Practice, The Journal of Legal Medicine (July/August 1974).

Drug Substitution -- Boon to Consumers Versus Legal Trap for the Professional, The Journal of Legal Medicine (March 1976)

Recent and Pending - Drug Regulatory Legislation - Survey and Overview: Proceedings, Management Science Conference for the Pharmaceutical Industry, Purcue University, West Lafayette, Indiana (September 20, 1976)

DR. JOHN G. ADAMS

Born January 31, 1921, in Pittsburgh, Pa. Educated in Pittsburgh Public Schools; B.S. in Pharmacy, Duquesne University, 1947; M.S. (Pharmacology) University of Illinois, 1952; Ph.D. (Major: Pharmacology; Minor in Medicinal Chemistry) University of Illinois.

During World War II served with 80th Infantry Division, Third U.S. Army, E.T.O., 1942–45. Bronze Star, Distinguished Unit Citation.

Owned and managed Adams Pharmacy, Pittsburgh, Pa., 1945–48. Instructor, School of Pharmacy, Duquesne University, 1947–49; Bristol Research Fellow in Pharmacology, College of Medicine, University of Illinois, 1949–52; Assistant Professor of Pharmacology, School of Pharmacy, Duquesne University, 1952–54; Associate Professor of Pharmacology, School of Pharmacy, Duquesne University 1954–55; Professor of Pharmacology, School of Pharmacy, Duquesne University, 1955–61; Assistant Dean, School of Pharmacy, Duquesne University, 1954–55; Dean, School of Pharmacy, Duquesne University, 1955–61; Professor of Pharmacology, School of Pharmacy, University of Connecticut, 1961–65.

Joined the Pharmaceutical Manufacturers Association staff in 1965 as Director, Office of Scientific Activities; Vice President, Scientific and Professional Relations 1968 to present.

Married to Mary Margaret Wagoner; two daughters. Biographical data may be found in *American Men of Science.*

Member of Phi Delta Chi (honorary) and Alpha Zeta Omega (honorary) Fraternities. Also member of Sigma Xi and Rho Chi Honor Societies.

Memberships are held in the American Pharmaceutical Association, Americau Association for the Advancement of Science (Fellow) and New York Academy of Sciences.

Member, Executive Committee, American Association of Colleges of Pharmacy, 1959–61; Vice Chairman, House of Delegates, American Pharmaceutical Association, 1960; Chairman, District 2 Boards and Colleges of Pharmacy; Vice President, Rho Chi Society, 1963–65; National President, Rho Chi Society, 1966–68; Chairman, Committee on Permanent Organization, American Pharmaceutical Association, 1960–63; Committee on Curriculum, American Association of Colleges of Pharmacy, 1956–1959, Chairman, 1957–59; Executive Committee, Pennsylvania Pharmaceutical Association, 1955–1961; Committee on Predictive Tests, American Association of Colleges of Pharmacy, 1959; Joint Committee on Hospital Pharmacy, American Association of Colleges of Pharmacy—American Society of Hospital Pharmacists, 1959; Committee on Student Chapters, American Pharmaceutical Association, 1961; Committee on Selection of Recipients, American Pharmaceutical Association Foundation Awards, 1961; Governor's Advisory Committee on Civil Defense, Commonwealth of Pennsylvania, 1960–1961. Visiting Lecturer, American Association of Colleges of Pharmacy, 1963–1965.

Dr. PIECZENIK. I find that you can find scientists on either side of any issue. Therefore, let the scientists lobby and let it be decided by a representative of the public.

Mr. THORNTON. If scientific fact is to be demonstrated by debate before a lay public body, which then announces the decision as a jury would announce a decision, then I am very concerned that the possibility that the truth is not represented by either side of the issue may be overlooked. By characterizing scientific arguments as the opposition of a right and a wrong position and deciding between those two positions, if that is the basis for developing the field of scientific knowledge, I am very concerned about it.

I think that is the way to develop dogma.

Dr. PIECZENIK. There is not a right and a wrong position. There is a position of those that wish to do the experiments and these are not scientific issues that are being questioned.

These are basically moral, whether the experiments should be done. Since it is a moral, a political issue, let it be a moral, political body that decides it.

Mr. THORNTON. I think, that insofar as these issues relate to moral, political, and philosophical judgments, that all segments of society must be involved. But I would be most hesitant to assume that those people who are most knowledgeable about the subject matter should be excluded from that process.

I find that very hard to accept. I think that we should review their contribution with a great deal of care and concern, in view of the fact that it might be biased, and to try to overcome the possibility of such bias.

I did not mean to get into an argument with you about it. But I was concerned about your suggestion that the people most knowledgeable should be excluded from the board.

Dr. PIECZENIK. Well, I question whether—I will accept that. The question of knowledgeability in an unknown area—there is no expertise in an area that has not been experimented in. Everybody's opinion is as good as everybody else's.

Mr. THORNTON. Everybody is starting pretty much even.

Dr. PIECZENIK. At this stage, let's give the public a chance.

Mr. THORNTON. I see.

Thank you.

Do any of you have any further comments? [No response.]

I want to think you. The response has been stimulating, way over my head most of the time, and I think it has really given us some material which our strong staff can assimilate and report back to us in language we can understand.

Thank you very much.

Dr. PIECZENIK. Thank you, Mr. Chairman.

Dr. RYAN. Thank you.

Dr. CHARACHE. Thank you, Mr. Chairman.

Dr. FORMAL. Thank you.

Mr. THORNTON. We are adjourning to reconvene tomorrow at 10 o'clock in this room to discuss those aspects of this issue which are of concern to industry.

We are now adjourned.

[Whereupon, at 12:30 p.m., the subcommittee adjourned, to reconvene at 10 a.m., Thursday, April 28, 1977.]

Each country has its own plasmids and they work according to guidelines under which they want to work. It is a logical constraint. I do think for the nature of the experiments, they are sufficient.

I think one P4 facility can be built and all the experiments can be booked there. This is much like you book a cyclotron. I think money should be spent in other types of research.

Mr. HOLLENBECK. I see we are running late. I don't know what everyone has on his schedule, but I would like to hear if anyone has a final comment to make, or a comment on something someone else has said, or something we may have overlooked in our questioning. We would welcome that at this time with the Chair's permission.

Mr. THORNTON. Yes; I think that is very appropriate. I did notice that Dr. Ryan perhaps has a commitment for which he may already be late. Therefore, I would invite you if you have any concluding remarks to state them, and then you may be excused.

Then we will let each of the other witnesses have such remarks as they may have.

Dr. RYAN. The only thing I would ask is a clarification. I assume that by asking for a generalized and lay review that you are not excluding peer review in this process? In my own personal opinion, you require both. I think you need somebody to make the judgments on scientific ground and I think you then need a broader committee to make judgments on moral and ethical issues.

Dr. PIECZENIK. Scientific judgment will be made by the committee presenting the experiment.

Mr. THORNTON. Dr. Ryan, I have just been advised that the person with whom you are scheduled to have a meeting is not going to be available for that meeting right now. You may want to stay aboard for awhile.

Dr. RYAN. All right.

Dr. CHARACHE. I have one comment on one of the points made by Dr. Pieczenik. I think it probably would not be wise to require that the responsible senior investigator be the one to wield the equipment because a highly trained technologist can often do a much safer job of it than perhaps the old scientists.

I think the critical thing here is a sense of responsibility on the part of the scientific community and on the part of the people who are insuring that the motives of the scientists are, in fact, met by their practical approaches.

Mr. THORNTON. I think that that is a useful observation.

Dr. FORMAL. I would just agree with that.

Dr. PIECZENIK. I disagree. In England, it is the senior scientist that does the work. Brenner designs his vectors himself. Sanger sequences. I think that tradition should be brought to this country. On the other hand, in tradition where the experiment is left to a technician, the freedom of choice is gone. I think he should have a choice.

Mr. THORNTON. I rather doubt that this particular issue will be addressed by legislation, but it is a very interesting element of public policy. I would hate to deprive science, though, of an individual's mental capacities because of his lack of physical capacity actually to carry out certain thinking processes.

I would assume that you would agree that such situations may be possible—you would not?

"clean hands." You don't enter the court having committed a crime in the area in which you are suing for justice.

I would like a clean-hands legal policy basically for the regulators as well as the experimenters; meaning that there is not a clear or vested interest that this experiment work.

That is eight personal, financial or for scientific reputation.

Mr. HOLLENBECK. I am very interested in your second topic. You look to a lot of public input from different segments of the public, whereas we have heard a lot of testimony so far suggesting that the GMAC consist of scientists who are engaged directly in this work. I wondered why you have chosen that?

Dr. PIECZENIK. I believe in the people. The other thing is that basically science is tax money. It is people's money. There is no accountability. Are we publishing paper monuments to our own research? What is the accountability on the research? Let us say this does not work. At what point do you say look, this has been a waste of money? Or, what happens to the equipment that is given to researchers by NIH after the researcher retires? That stays in various laboratories and never gets recycled.

I am not sure whether there is a class of scientists. But in any case those working in research receive public money and therefore there should be public accountability. None of these issues are that complex and if they are complex, if they are clearly understood, they can be explained.

Mr. HOLLENBECK. I see some disagreement at this end of the table, Dr. Formal.

Dr. FORMAL. I have worked for 25 years as a research scientist in a Federal laboratory. During this time public funds for research have increased tremendously. At the outset, we had few experienced scientist-administrators. Over the years, we have been fortunate to have many capable scientists become experienced administrators, and as a laboratory worker, I respect their achievements. A worker doing fundamental research is held accountable for his work, and I think that most laboratory workers believe that we owe a great debt to the public for supporting our endeavors.

As funds get shorter and competition for funds get more keen, that accountability will become better also. I am really not discouraged over this. I think most of us feel certainly over the past 10 years a great debt to the public.

Dr. CHARACHE. I would agree with that. I have seen this operating also in our own institution and at the National Institutes of Health where a peer review concept is being explored for the work that is done intramurally even though this is not formally required.

I think there is an increasing desire to be sure that the investigator is accountable. I think the same is true in terms of the management of the NIH guidelines. Not everybody on the committee of biohazards has anything to do with recombinant research.

Other people have responsibility to be sure that the scientists have considered all aspects of the work. The responsible scientists have been foremost among those who wish to be responsible. They are the ones at greatest personal risk.

Mr. THORNTON. Pursuing that line of thought for a moment, were you as careful in this type of research before the NIH guidelines were announced as you are now? Do you think that the mere presence of NIH guidelines, even for scientists not [illegible]

tern of about 200 nucleotides. The nonhistones protein might be involved.

Ninety-nine percent of DNA is not coding at all. One can ask the question why? Ninety-nine percent of the DNA isn't even made into messenger RNA. We will be looking at a universe of DNA.

Mr. THORNTON. I wish you would have said that in the first place.

Dr. PIECZENIK. We are only looking at 1 percent or maybe 2 or 3 percent of what exists at the DNA level in terms of protein function.

Dr. RYAN. Suppose you did put in a piece of DNA and it wound around the histone, would that DNA be expressed?

Dr. PIECZENIK. In what, the eukaryotic systems?

Dr. RYAN. Yes.

Dr. PIECZENIK. I would guess not. I would think that the transcription start signals are quite different. The question of whether a promoter exists in these sequences is unknown. At the prokaryotic levels, it is a contiguous set of signals prior to the messenger RNA. It could be ectopic DNA fibers that link various chromosomes together and you activate them and several chromosomes simultaneously.

The whole question of that is completely unknown at this stage.

Dr. RYAN. What that would imply is that prokaryotic DNA got transferred to a eukaryotic, it might not be expressed and might not be as hazardous as you might first think?

Dr. PIECZENIK. That is right. However, the sequences have a history—they still have "gill slits". Ontogeny recapitulates phylogeny. That is reflected in our development. These sequences might reflect the same type of sequence.

These might be reactivated. There might be prokaryotic type sequences in eukaryotic DNA. When you put them into prokaryotic systems, they might be expressed. In fact there have been experiments done where you can take prokaryotic messenger RNA and bind them to eukaryotic RNA and it will recognize the same binding sites as the prokaryotic.

However, if you go the other way, take eukaryotic messenger and give it to prokaryotic ribosomes, they will not bind.

They will not be recognized. So the signals may go in one direction and not in the other.

Mr. THORNTON. Isn't the basic point here that you are dealing with a subject matter which is so complex, where the potential combinations are so immensely variable that the field of ignorance about the process is much larger than the field of knowledge at this stage?

Dr. PIECZENIK. That is true. In research, the idea is to be at the front lines and to be ignorant at all times. You should not know anything but you should understand everything.

It is not answering the question, it is first defining the problem. Once we can define the problem, answering the question becomes simple. The cure to cancer is a poorly defined scientific problem. That is why we don't have an answer. The moment that problem is defined, then there will be an answer.

Mr. THORNTON. I want to recognize Mr. Hollenbeck for some questions. This has been a fascinating discussion, but I would like to give him an opportunity to lead the discussion for a time.

Mr. HOLLENBECK. Mr. Chairman, I have a question of Dr. Pieczenik which involves his suggestion with regard to regulation of recombinant

Mr. THORNTON. Dr. Ryan, would you comment on this line of questioning?

Dr. RYAN. My comments are based purely on what I have read. I have no practical experience. It seems to me that they are adequate as near as I can judge. I would say in response to the last question that if somebody is going to deliberately misuse the guidelines, they are going to misuse them, and there isn't very much you can do about it.

Dr. PIECZENIK. The possibility of doing the worst experiment can be done for about $150. You can buy SV40 DNA commercially for about $30. You can buy the plasmide for about $30. You can buy the restriction enzymes for $55 and you can shotgun it into the colony in about 3 hours.

So all the components are commercially available to do the worst experiment.

Mr. THORNTON. I think perhaps one of the greatest inhibitions against the selection of this particular technique by terrorists is the fear that they might be their own first victim.

Dr. PIECZENIK. Given my perspective, it would not work anyway.

Mr. THORNTON. The hazard of self-destruction might be one. Then I think some consideration would have to be given as to what other tools might be available, having a more predictable result.

Dr. PIECZENIK. Sidney Brenner in Cambridge is trying to adapt E. coli to live in an environment of heavy water, rather than a naturally occurring water. If he can adapt an E. coli in that manner, the chance of that escaping and finding an ecological niche is very rare. The refined approaches to the types of vectors used—but let us say carefully and genetically designed vectors would be more appropriate.

Mr. THORNTON. If I may pursue the terrorist point to my next question which concerns some inadvertent recombination might unlease a catastrophic situation by developing an organism or a process which is not yet known. I think your testimony is appropriate to that discussion.

We have been told by other witnesses that this is a significant risk. It is one we are concerned about. Would you address yourself to that question?

Dr. PEICZENIK. At present I feel that as I said before, the possibility of direct expression is unlikely in extreme species crosses. If you design a vector or a virus carefully, and in time we will be able to know how to design one, that can bypass or accommodate the intracellular selection, then, the possibility of an artificially engineered virus that is viable and can be used as a weapon or a tool becomes quite likely.

But I would say that this is 10 to 15 years away.

Until we understand the sequences and their advantages, we won't be able to design it.

Mr. THORNTON. Are you saying it would not likely occur accidentally but only through a long purposeful design?

Dr. PIECZENIK. With purposeful design, I imagine it is possible. Without design I feel it is unlikely.

Mr. THORNTON. I think this is an area in which there is a good deal of concern expressed and maybe disagreement as well. Dr. Ryan?

Dr. RYAN. One of the areas that is of great interest in endocrinology today is the matter of gene expression and the role of steroid hormones in inducing gene expression. This seems to be related in part at least

fact that the host which is being used for this experimentation is a variation of a bacteria which does exist within the human system.

I think I understand that the reason that this particular host is the subject of experiments is because it is well understood and predictable, and varieties have been developed which have low survivability.

Still, how would you address the question of whether this is the appropriate microorganism for use in this kind of research? Should there be some thought given to perhaps selecting another organism? There are a lot of lay people who might be more comfortable if experiments were being conducted on nitrogen fixing bacteria that infect plants rather than with *E. coli.*

Dr. FORMAL. Certainly other organisms could be used and of course this possibility should be pursued. Nonetheless, geneticists have had 30 years of experience working with this K–12 strain. I believe that it would not be wise to discard these 30 years of experience.

Mr. THORNTON. I am not suggesting that that should be done.

Dr. CHARACHE. There is so much known about *E. coli.* It is often safer to use what you know and understand than what you are guessing about. When you can construct variants that will not survive outside of the laboratory because of your knowledge of the organism and you know what its stability is, it becomes much safer to use than using something that you don't know about.

Dr. PIECZENIK. Did it try K–12 with the plasmid containing antibiotic resistance markers?

Dr. FORMAL. These experiments were done by Dr. Anderson using E. coli K–12 strains carrying either transmissible or nontransmissible plasmids which code for tetracycline resistance.

Dr. PIECZENIK. Has this bacteria been able to colonize in a patient taking tetracycline?

Dr. FORMAL. That has not been done.

Dr. PIECZENIK. Don't you think it would be able to colonize?

Dr. FORMAL. I do not know. It is an experiment which will have to be done before one can get an answer.

Dr. PIECZENIK. Would not K–12 containing antibiotic resistance survive better?

Dr. FORMAL. It might, but that is an experiment which will have to be conducted.

Dr. PIECZENIK. In the experiment, in which the bacteria was possibly shown to contain mammalian product, the bacteria should not have been growing in the media. There was antibiotics in that media. That means that the bacteria was resistant to the antibiotics. Antibiotic resistant bacteria adapt, and they have quite a capability to survive in our world. In fact, I would think the use of antibiotic resistant plasmines as a vector is uncalled for; because you give the bacteria an environment that is already saturated with antibiotics.

Mr. THORNTON. I think that is a very useful observation.

The use of a plasmid containing other bacteriological resistance would not be beneficial. However, I do think it is also interesting to note, as has already been mentioned, that genetic engineering of sorts has been accomplished by growing bacteria in atmospheres which contain antibiotics and thereby causing selected bacteria to develop resistances to those antibiotics and to change genetically.

than was the wild-type K–12 strain administered by Dr. Anderson to volunteers in England.

Additional studies are required prior to concluding with confidence that *E. coli* K–12 or derivatives of it such as 1776 cannot multiply and survive within human intestines and within other hosts. Nonetheless, the complexity of this process predicts the necessity of a multitude of genes, all functioning in concert, which confer upon bacteria such ability for survival.

We know that a large number of laboratories have worked with a wide variety of highly virulent and contagious micro-organisms which as pathogens have this capacity to survive. On the basis of past experience, there has been no evidence of spread of any disease to the surrounding communities.

There is no reason to believe that laboratory altered strains of the already weakened *E. coli* K–12 will escape from a proper containment facility to the population at large.

[The documents referred to follow :]

TABLE 1.—DURATION OF SHEDDING FOLLOWING INGESTION OF E. COLI STRAIN HS BY HEALTHY VOLUNTEERS

	Dose (cells)	Duration of excretion (days)
Volunteer:		
1	1×10^{8}	12
2		0
3		16
4		60
5		45
6	1×10^{10}	105
7		21
8		7
9		24
10		75

TABLE 2.—DURATION OF SHEDDING FOLLOWING INGESTION OF E. COLI K–12—SHIGELLA FLEXNERI HYBRID STRAIN

	Dose (cells)	Duration of excretion (days)
Volunteer:		
1	1×10^{8}	0
2		0
3		3
4		4
5		3
6	1×10^{10}	0
7		5
8		4
9		4

Dr. FORMAL. On table 2, patient 6 should be 10 to the 10. Thank you very much.

Mr. THORNTON. It has been suggested that the lack of identifiable spread from these facilities may be because insufficient records were kept. Do you have any comment about that?

Dr. FORMAL. Spread of nonpathogens would be difficult to monitor. However, scientists in the United States have worked, over the years, with a wide variety of highly virulent and highly infectious agents. Although laboratory accidents have occurred, infections of the population in the vicinity of these laboratories have not been reported. Considering the ease which infectious agents can be detected, they

we finish hearing Dr. Samuel Formal, Chief of the Department of Bacterial Diseases, Walter Reed Army Institute of Research.

We are very pleased to have you with us today. We are looking forward to your testimony with anticipation.

[A biographical sketch of Dr. Formal follows:]

DR. SAMUEL BERNARD FORMAL

Born: August 28, 1923, Providence, R.I.
Education:
Classical High School, Providence, R.I., 1941.
Brown University, A.B., class of 1945.
Brown Uuiversity, ScM, 1948.
Boston University, Ph.D., 1952.
Military service: U.S. Navy, 1943–46—Lieutenant (junior grade).
Married: Rosamond Anne Martiu (A. B. Smith, 1947, ScM Brown, 1949) October 27, 1951.
Children: Christopher Stuart, born 1953, David John, born 1955, James Martin, born 1959.
Positions held:
Bacteriologist, Food and Drug Administration, 1948–49.
Microbiologist, Walter Reed Army Institute of Research, 1952–56.
Chief, Department of Applied Immunology, WRAIR, 1956–76.
Chief, Department of Bacterial Disease, 1976–
Memberships:
American Society of Microbiology.
American Association of Immunology.
Americau Association for the Advancement of Science.
Society Experimental Biology and Medicine.
Sigma Xi.
Infectious Diseases Society of America.
Boards and Commissions:
American Academy Microbiology.
Professional Lecturer, Georgetown University Schools of Medicine and Dentistry.
Editorial Board, American Journal Epidemiology, 1966–72.
Commission on Enteric Infections, Armed Forces Epidemiological Board.
WHO Scientific Group on Oral Enteric Bacterial Vaccines.
Editorial Board, Journal of Reticulo-Endothelial Society, 1974–
Project Director, U.S. Army Enteric Diseases Program, 1972–
American Academy of Microbology, Civil Service Subcommittee, 1972–75.
Board of Civil Service Examiners, 1968–

STATEMENT OF DR. SAMUEL FORMAL, CHIEF, DEPARTMENT OF BACTERIAL DISEASES, WALTER REED ARMY INSTITUTE OF RESEARCH

Dr. FORMAL. Thank you, Mr. Chairman.

I am Samuel Formal of the Walter Reed Army Institute of Research. I was educated at Brown University and received a Ph. D. degree from Boston University. I am a laboratory research scientist who works on diarrheal disease.

I have been asked to discuss the potential of *Escherichia coli* to cause disease. Organisms belonging to this genus are present in competition with many other micro-organisms belonging to the intestinal tracts of many animal species and of virtually all human beings.

The usual levels of *E. coli* found in normal human adults is approximately 1 million to 10 million cells per gram of feces.

They are by no means the predominant organism in the intestinal tract and make up less than 0.1 percent of the flora. Studies have shown

like illness in man that is being extensively studied. Most bacteria cause illness——

Mr. THORNTON. May I interrupt just for a question at that point? Is the theory that the *E. coli* is modified by the introduction of a plasmid in order to produce that type of illness by some natural means?

Dr. CHARACHE. Yes.

Mr. THORNTON. Thank you. Please continue.

Dr. CHARACHE. The type of disease produced which can cause either a localized infection or a general systemic disease is in part a function of the microbe and due to species characteristics of the organism, and in part due to the individual patient and the relationship he establishes with that microbe.

The organism can gain entry through a number of routes. They can be inhaled. They can be ingested. They can penetrate the skin either directly or through a cut or puncture. Laboratory accidents may involve any of these routes and, as you know from previous testimony presented here, such accidents have occurred in a number of instances.

E. coli, although they have been among the most extensively studied organisms have rarely presented laboratory problems either in the research laboratory or in the clinical laboratory because it is so rarely pathogenic to normal man.

Laboratory technicians in clinical laboratories such as ours at Johns Hopkins will process tens of thousands of specimens of *E. coli* on open benches under P_2 laboratory protective conditions, and, because of the nature of the organism, we do not have an infectious disease problem in the laboratory.

Healthy adults, exposed to this organism in the laboratory setting, have not had problems with it. Normal healthy volunteers who were fed the virulent strains of *E. coli* have been shown to colonize with this more virulent strain only if massive numbers of organisms are ingested.

These strains have been shown to be usually shed by the people who ingest them between 1 and 10 days after ingestion. In reviewing a bibliography of over 1,500 laboratory accidents in which infection was reported, I found one report in which *E. coli* was incriminated and this was with a toxogenic strain. One case was reported of a worker who developed a diarrheal disease associated with a toxogenic strain 1 year after this had been isolated from some travelers.

The *E. coli* created to the recipient strains in DNA recombinant research are being engineered to be variants that are far less virulent than wild-type strains and they are designed to fail to survive outside the laboratory.

I would like to emphasize that genetic recombinant standards are not new, nor is genetic recombinance limited to laboratory experiment. Twenty-five years ago, before DNA had been fully characterized, a semipurified DNA was shown to pass genetic characteristics between organisms.

Twenty-five years ago, experimenters deliberately designed their studies to require the use of safe biological markers.

It became recognized also that bacteria normally exchange genetic information under natural, nonlaboratory conditions. Thus for example, wild-type spread of information between bacteria has resulted in major medical problems at the present time.

Mr. THORNTON. It is very interesting how research in another area could lead you to the field which is the subject matter of these hearings. Furthermore, this resulted in your needing to isolate the product in order to test whether the bacteria has the capacity of producing a mammalian protein, to require the tools used in DNA recombinant research in order to evaluate whether or not that characteristic is or is not present.

I think that is an interesting bit of information in itself, quite apart from the resolution of the question before us.

Dr. RYAN. There is a point with respect to that that I would like to make although it is somewhat irrelevant to this committee. It is very difficult to predict where scientific discovery is going to come from. I think one of the tendencies on the part of Congress has been to channel money into rather highly specific areas like cancer and various other diseases. I think one of the consequences that financial support in basic areas of research where the serendipituous event is more apt to occur, tends to be restricted. I hope that you and your colleagues can bear that in mind.

Mr. THORNTON. When you speak of serendipity I think that often we need to be able to discover what we had not expected. After all, that is also a part of scientific inquiry, not only to look at the results that were the major reason for doing the experiment, but also to observe other things that happen and to ask why those things happened. And maybe not to accept any particular theory as being unequivocably true in making that kind of inquiry.

The thing that also struck me as I read and listened to your testimony was the question of mimicry which you alluded to. We have had some good testimony in other hearings before this subcommittee about surface phenomena, the properties of certain atoms and molecules that act as receptors to hold or to cause certain patterns to develop which can then be used in various ways.

Do I understand properly from your testimony that a possible theory is that such a pattern may exist in connection with this bacteria which causes facsimilies of the mammalian protein to attach themselves or to be produced?

Dr. RYAN. Yes, I think this is a possibility. You can think about it in this way. There is a lot of diversity in nature, but probably nature has a limited number of ways of doing certain things. For example, in these protein hormones that we have just discussed, there is an amino acid sequence that turns out to be identical to an amino acid sequence that is present in cholera toxin and all of the serine protease enzymes. We don't know the purpose of this common sequence in these diverse proteins. It is conceivable that there are limited numbers of ways in which a protein can interact with another protein or interact with something else like a cell surface receptor and thus this common sequence, mimicked, if you will, in a variety of proteins, may serve a very common purpose. There may be limited numbers of ways in which a protein will bend itself and it might require a common amino acid sequence in order to do that bending.

Mr. THORNTON. Thank you. Mr. Hollenbeck?

Mr. HOLLENBECK. At page 2, you said you asked why these bacteria have a binding site for a mammalian protein hormone. Are you sug-

Despite this skepticism, there is one point with respect to our data that we cannot explain and some additional observations from the literature for which the data are insufficient to offer an explanation. First, we have observed radioimmunoassayable hCG activity in some batches of culture media, even in the presence of protease inhibitors. Second, there are no data to say that the explanations offered above apply to the organisms isolated by Doctor Livingston or Doctor Cohen.

We simply do not have conclusive proof that the Pseudomonas maltophilia organism has or does not have the DNA for making the mammalian hormone hCG. The same may be said for Progenitor cryptocoides or epidermal staphylococcus. We have, therefore, begun studies to obtain this proof. These studies take two forms:

1) A Pseudomonas maltophilia culture has been sent to Dr. Stuart Levy of Tuft University who will analyze for the presence of a plasmid. If a plasmid is found, it will be tested for hCG production and hCG-binding activity.

2) Dr. Ronald Cox of our Department at Mayo is preparing the mRNA for hCG from placental tissue. He will then prepare radioactive cDNA to the mRNA. The binding of the labeled cDNA to Pseudomonas maltophilia DNA will then be tested and should give evidence for the presence or absence of the mammalian genome. The same cDNA can be used to test the other organisms that have been reported to produce hCG.

It should be mentioned that hCG is not the only candidate that may be implicated as a possible example of a natural recombinant DNA. The hCG binding site is also a possibility as are a variety of mammalian antigens found on bacterial surfaces (see Markowitz, Trends in Biochemical Science 1,161, July, 1976, for a review).

Doctor Cohen originally described this as a gram-negative motile rod that was not further classified. He has subsequently told me in a personal communication that the organism is the same as that isolated by Doctor Livingston and is classified as an epidermal staphylococcus.

Our own studies on the culture media from Pseudomonas maltophilia have yielded the following information:

1) Culture media caused a dose-related decrease in the amount of ^{125}I-hCG bound by antibodies to hCG or the β subunit of hCG.

2) Culture media caused a dose-related decrease in the amount of ^{125}I-hCG bound by rat ovarian receptors for hCG.

3) Culture media, at low doses, stimulated the rat ovarian adenylyl cyclase enzyme in a manner similar to hCG but at high doses caused a loss of the activity of this enzyme.

4) Culture media clearly stimulated progesterone production by immature rat ovaries, in vitro, on one occasion. On other occasions the stimulation of progesterone production has been questionable.

These observations prompted us to believe that the bacteria were indeed producing an hCG molecule and led to two additional lines of investigation. The first was an effort to isolate the molecule with hCG activity from the bacterial culture media. The second was to determine if the bacteria contained mammalian DNA capable of coding for hCG or hCG receptor.

Attempts at purification of the hCG-like material from the culture media were marked by a number of inconsistencies. First, there

BACTERIA AND HUMAN CHORIONIC GONADOTROPIN

Dr. Nancy D. Richert, working in my laboratory, undertook a study of rat ovarian cells grown in tissue culture specifically to determine their ability to bind radioiodinated luteinizing hormone (LH) or human chorionic gonadotropin (hCG). These glycoprotein hormones regulate specific ovarian cells and induce them to produce the steroid hormone, progesterone, which is required for the maintenance of pregnancy. A variety of purified materials were added to the culture media in an effort to maintain hCG binding activity, but to no avail. Crude mixtures derived from various biologic sources were then used and one of these was ovarian follicular fluid, obtained from pigs. The cultures containing follicular fluid showed excellent binding of hCG even after being grown in a flask for 5-7 days.

Subsequent examination of the follicular fluid containing cultures revealed that hCG binding was not to the rat ovarian cells but to a contaminating microorganism. The organism was isolated and identified as the bacterium, Pseudomonas maltophilia. Since the binding of a protein hormone to a microorganism had not been found previously, we decided to study this phenomenon.

The results of this study were published in the March, 1977, issue of The Proceedings of the National Academy of Sciences, U.S.A. These findings indicated that the bacteria specifically bound hCG and hCG-like molecules with characteristics similar to, but not identical with, hCG receptors (or binding sites) found in ovarian and testicular

Is that a conclusion based upon the answer to the chairman's last question?

Dr. PIECZENIK. It is a conclusion based on the concept that there is a competition of molecules and also the belief that cloned DNA does not have a competitive advantage over natural DNA in its milieu and the observation, now, that no cloned DNA has had faithful expression and extreme species crosses into a plasmid have had no expression. The hemoglobin gene that was put in a plasmid did not make hemoglobin. So far there is no evidence, and it has been 5 years of experimental work, that there has been faithful or proper expression of the DNA.

That does not point out the fact that small polypeptides—small functions that could have functioned once, isn't happening. Small polypeptides seem to have powerful functions. Things that you don't expect to be made, become the hazard, not the things you do.

Mr. THORNTON. I think it might be useful if we go ahead and hear the other witnesses and then open the hearing to discussion with the entire panel. Can each of you stay aboard for that schedule? I appreciate that.

Next, I would like to introduce and call upon Dr. Robert J. Ryan, of the department of molecular medicine of the Mayo Medical School. Dr. Ryan has had a distinguished career and has made some discoveries which may or may not—and I am not sure what the testimony will be or the ultimate outcome will be with regard to that question—be examples of natural recombinant DNA.

We are very pleased to have you with us. We look forward to your testimony.

[A biographical sketch of Dr. Ryan follows:]

DR. ROBERT J. RYAN

Academic rank: Professor.
Mayo appointment; July 1, 1967. G.S. Status: B.
Medical field: 1.
Section assignment: MOLECMD 50 A.
Date and place of birth: July 18. 1927, Cincinnati, Ohio.
Retirement date: September 1992.
College/medical school training with degrees and institutions conferring them:
Xavier University, Cincinnati, Ohio, January 1945 to October 1945.
Xavier University, Cincinnati, Ohio, February 1947 to August 1948.
University of Cincinnati, Cincinnati, Ohio. M.D., September 1948 to June 1952.
Internships: Henry Ford Hospital, Detroit, Mich., July 1952 to June 1953.
Residencies:
University of Illinois, Chicago Ill., July 1953 to June 1954.
Resident and educational hospitals, Chicago, Ill., July 1954 to June 1956.
Resident and educational hospitals, Chicago, Ill., Chief resident, July 1956 to Jnne 1957.
Tufts University, Boston, Mass., July 1957 to September 1958.
Professional preparation/academic experience:
University of Illinois, instructor in I, July 1956 to June 1957.
University of Illinois, assistant professor of I, January 1958 to September 1963.
University of Illinois, Associate professor of I. September 1963 to July 1967.
Mayo Clinic, consultant in physics. July 1967 to January 1968.
Mayo Graduate School, associate professor of I, January 1968 to July 1971.
Mayo Graduate School, professor of I, July 1971 to March 1973.
Mayo Medical School, professor of I, March 1973.
Intramural activities:
Research committee, vice chairman, 1972–.
Building committee, research liaison, 1974.
Molecular medicine, chairman department, July 1974–.
Research committee, 1970–1971.
Endocrine research, chairman department, November–July, 1971–1974.

Three: The background of members of the scientific advisory board be investigated to make sure that they do not have a history of morally repulsive experimentation. Nor should they, like Caesar's wife, give the appearance of wrongdoing.

Four: In order to avoid coercion within laboratories I would suggest a head of laboratory rule. That is, the principal investigator of the grant have the legal and direct responsibility of doing the actual DNA restriction, mixing, ligasing, insertion, and transfection if a plasmid is used; of infection if a phage vector is used. This responsibility should not be an assignable one. This will allow those that do not want to do the experiment, the freedom to decline. The organizational structure of funding at the present time does not allow the freedom to decline. This will also force more careful thought in design of the experiments and hazards.

In summary, my perspective of genotypic selection suggests that the first experiments that should be done are those that test the intrinsic mutability of cloned DNA and the fidelity of its expression.

These can be done without hazard or cost. Unfortunately, the scientific establishment in the United States has the financial constraint which makes it unlikely that the cheapest experiments will override the more expensive; or the disposable experiment override the capital intensive one.

However, this is, uniquely my perspective, based on a study of naturally occurring nucleotide sequences. The contemporary view of all molecular biologists, especially those that have appeared as witnesses is that the expression of DNA is universal and passive. It is to them a piece of instruction and its expression is unaffected by the mechanism of expression. Time and more research will tell.

As a slight digression, if genotypic selection exists then Donald Fredrickson is wrong and a magic bullet for cancer is possible, but that is another story.

Thank you.

Mr. THORNTON. Thank you very much, doctor. This is the first time that a witness has given a statement more rapidly than I could read it. That is a new experience. I do commend you for a very scholarly presentation. I would like to ask you, with regard to your statement that evolution and not DNA is the basic dogma of life and biology, whether you are tending to exaggerate that by characterizing those studies as dogma.

I personally do not like to assume a dogmatic position. I think that tolerance of views is necessary, that the difference between the Darwinians and the non-Darwinians may not reflect that either is wrong, but that both may be partly right, and partly wrong.

I wondered if you would like to clarify that statement to any degree? Was it an overstatement, or do you think that it is an article of faith?

Dr. PIECZENIK. Yes. In biological research evolution is an article of faith. You explain phenomena in biochemical observations in terms of their adaptiveness. That is why we can say: Why does this molecule exist here? We can ask why questions because we believe that there is a dogma of evolution.

Otherwise we would ask questions of sodium chloride, table salt. One does not ask why do we have salt. But we can ask why do we have collagen as a structural protein?

We can now ask ourselves the same question about artificially inserted DNA sequences, "Does the insertion of a foreign piece of DNA confer an advantage or is it neutral to the ability of DNA to replicate?"

The data Darwin was working with was basically descriptive gross morphology of organisms; the data Kimura worked with was protein sequences, which he considered a phenotypic measure. Both however would predict, but for exactly opposite reasons, that if one could examine nucleotide sequences directly they would be random.

The Darwinian rationale is that the variant is a historical accident that worked, as well as the observation that there are so many steps between the mutation which is considered to be random and its expression as an adaptive phenotype that essentially the complexity make the relationship between nucleotide order and phenotypic adaptiveness intrinsically nonpredictive and random.

The non-Darwinians believe that every mutation occurs randomly and is expressed, if neutral, and survives in a population as a consequence of random drift.

Almost all molecular biologists, geneticists, and biochemists fall into a spectrum between these two views, depending on whether they think about this question in the first place. Evolution is the basic dogma of life. DNA sequences must find their proper place in evolution.

If Darwin had lived in this generation, he would have had access not to finches on the Galapagos Archipelago but to DNA nucleotide sequences. That is, if Darwin had direct access to genotype instead of to phenotype would he have seen them as random? Or would he have seen patterns of similarities between species as well as variability of sequences within species?

My contribution to molecular evolution was to study both the Darwinian and non-Darwinian approach and to disregard their certainty in the essential randomness of nucleotide sequences and approach nucleotide sequences as Darwin might have.

I was able to find evidence for various types of patterns at the nucleotide sequence level. These patterns I called constraints or restraints depending on whether the pattern was a consequence of syntactical function or structural function. Examples of such patterns are the simple symmetry pattern of palindrome—AUUAAAGUUG-AAAUUA—the internal terminator constraint, and the recently published constraint on messenger RNA sequence as a consequence of a postulated tRNA interaction which makes the genetic code a partially overlapping triplet code.

The last constraint implies that though the genetic code is universal, messenger RNA translation is species specific.

In order to explain the existence of these patterns at the nucleotide level it was necessary to postulate the existence of a specific type of selection which acts at the nucleotide level. Whereas natural selection is predominantly phenotypic, the existence of order at the nucleotide level suggests that there is a natural selection that is genotypic. This I call genotypic selection.

In genotypic selection it is the DNA molecules themselves which compete for their substrates, their ability to be replicated, transcribed and translated. This type of selection occurs in the intracellular milieu.

Genotypic selection imposes structural as well as syntactical constraints on nucleotide sequences. That each sequence is derived from

I am grateful to him that he came down here to address us and to the university for permitting him to do so. I would like to welcome him here today.

Mr. THORNTON. One of the colleagues of Dr. Pieczenik, Dr. Sidney Brenner, has recently been honored and has been selected as one of the 15 foreign scientists who are designated as foreign associates of the National Academy of Sciences.

Please proceed.

[A biographical sketch of Dr. Pieczenik follows:]

DR. GEORGE PIECZENIK

Born: December 19, 1944 in Havana, Cuba to Dr. and Mrs. Srul David Pieczenik.

Education: Phillips Academy Audoner 1961; Harvard University A.B. 1965; University of Miami M.S. 1967; New York Univ. Ph.D. 1972; Rockefeller University 1972–74; M.R.C. Lab. of Molecular Biology, Cambridge University—1970–1; 1973, 1974, 1976, 1977.

1975 to preseut: Assistant Professor, Department of Biochemistry, Rutgers University. The State University of New Jersey, New Brunwick, N.J. 08903.

Area of Interest: Genotypic Selection and nucleotide sequence analysis.

STATEMENT OF DR. GEORGE PIECZENIK, NELSON BIOLOGICAL LABORATORY, RUTGERS STATE UNIVERSITY, NEW JERSEY

Dr. PIECZENIK. Chairman Thornton, Representatives Hollenbeck and Dornan, members of the Subcommittee on Science, Research, and Technology, I would like to thank you for inviting me to appear as a witness before this committee.

I also have with me my brother, Steve Pieczenik, Deputy Assistant Secretary of State for Management.

Mr. THORNTON. We are pleased to have him at the hearing.

Dr. PIECZENIK. It is my understanding that the basic biology of DNA recombinant molecule research has already been reviewed and therefore I shall address myself to the scientific question of molecular evolution.

I will try to demonstrate that DNA recombinant molecule research is a form of artificial nucleotide selection nd therefore a question of *in vivo* molecular evolution.

On July 1, 1858, Darwin and Wallace presented a joint paper at the Linnaen Society describing their concept for the evolution of species. Wallace derived his concept by fevered inspiration, Darwin arrived at a concept of evolution of species by observing patterns of similarity between species and variations within species.

The similarity between species led him to the concept of descent from a common ancestor. We have taxonomic similarity to other life forms, because we all come from a common ancestor.

The variation within a species led to the concept of competition for resources and the survival of the fittest. These variants having competed and survived leave more progeny. These progeny carry the genetic characteristics that allowed their ancestor to survive in a particular environmental situation. This process Darwin called natural selection as opposed to artificial section.

At this point we can ask ouselves; if DNA recombinant research is a form of artificial human selection of nucleotide sequences, is there a natural equivalent process?

many other codons would be brought into play as these were demanded by mutation in the original rather simple messages.

Returning for the moment to the family of codons of the type $\overset{AAU}{GGC}$ notice that the two possible out-of-phase readings of this class of message given the codon sets $\overset{AUA}{GCG}$ and $\overset{UAA}{CGG}$. The former is related to the present start codons $\overset{A}{G}UG$ while the latter includes the present stop codons which are $U\overset{AA}{GG}$ if we ignore tryptophan (UGG) as being a later addition. Thus starting and stopping codons may originally have been evolved when the copying of the primitive message, with its restricted family of sequences, slipped out of phase.

8. Messenger Synthesis

Finally, we should consider how this original message, of the form ..., RRY, RRY, RRY, ... was synthesized. Apart from some repeated-slippage mechanism in the replication process a less obvious possibility is that the mRNA was initially formed *using the anticodon loops of the existing tRNA's molecules* as partial templates. This would be especially attractive if, under appropriate environmental conditions, there were a weak attraction between adjacent tRNA molecules and if tRNAs (without amino acids) could shift easily between the FH and the hf configurations.

Thus all that would be needed to get polypeptide synthesis started would be a single type of tRNA molecule to which a single amino acid was attached, though this would only produce a repeating homopolypeptide, such as polyglycine, from an equally simple message. By gene duplication and mutation (especially transitions) new, slightly different anticodon loops would be produced to pair with related codons and, hopefully, to attach to themselves new amino acids. Such simple pieces of chemical apparatus might well be enough to produce from a mutated message (or one synthesised by the mechanism suggested above) a few primitive proteins an occasional one of which might act to increase the accuracy and speed of the whole process. Given replication, natural selection could do the rest.

9. Concluding Remarks

Theories of the origin of life are usually fairly speculative and ours is no exception. The basic idea would be more credible if it could be shown that during present-day protein synthesis the tRNA does indeed occur in both the hf and the FH forms. At present the evidence on this point is weak and conflicting and so will not be reviewed here. If this flip mechanism turns out to be correct it may be possible to achieve template-directed synthesis in contemporary test-tubes without ribosomes by using (unmodified) tRNA molecules with carefully designed loops and having the appropriate amino acid attached to each one. This assumes that primitive tRNA molecules were very similar to present-day ones. The theory is thus to some extent open to experimental test.

References

Barell, B. G. and Clark, B. F. S.: 1974, *Handbook of Nucleic Acid Sequences*, Joynson-Bruvveri Ltd., Oxford.
Crick, F. H. C.: 1966, *J. Mol. Biol.*, **19**, 584.
Crick, F. H. C.: 1968, *J. Mol. Biol.*, **38**, 367.

the triplet part of the anticodon being in italics. Note that this symbolism does *not* imply that the message repeats exactly in groups of three but that the message must obey the purine-pyrimidine restrictions shown. Written out in full this becomes, for the mRNA

$$\ldots\ldots \begin{matrix}AAU\\GGC\end{matrix} \quad \begin{matrix}AAU\\GGC\end{matrix} \quad \begin{matrix}AAU\\GGC\end{matrix} \ldots\ldots$$

and 3′ $UG^{UUA}_{CCG}UU$ for the anticodon loops where $\overset{A}{G}$ represents A or G, etc.

The base pairs allowed are always either A = U, G ≡ C or G = U or their reversals. The pair A – C is *not* allowed, nor are A = G and G – C (see Crick, 1966).

Notice two points:

(1) This restricted base sequence although written with commas for convenience of illustration, is comma-free (in the sense of Crick, Griffith and Orgel, 1957), that is, a tRNA with any of the possible loops specified above cannot go onto such a message in either of the two incorrect phases and make five base pairs whether the loop is in the FH or the hf configuration. The advantage, at this stage of the problem, in having a comma-free code is not just that the message cannot then be read in the two incorrect phases (which would only improve efficiency by a factor of three) but that a tRNA cannot go onto the message, out of phase, just ahead of the growing point and either block the whole process or shift the phase of reading.

(2) The codons allowed are those found in the present code in the bottom right-hand corner (as the codon table is usually written) and stand for

GG^{U}_{C}	GA^{U}_{C}	AG^{U}_{C}	AA^{U}_{C}
gly	asp	ser	asn

so that, for example, the anticodon loop for the glycine tRNA would be

3′ UG*CCG*UU

This is encouraging as most people would be willing to believe that at least three of these (gly, ser and asp) are among the more likely primitive amino acids.

The assumptions of wobble in all positions produces an asymmetrical lack of precision. Consider the two triplets coding for asn which are AA^{U}_{C}. These will be read unambiguously by the tRNA for asn having the anticodon

3′ UG*UUG*UU

and by no other tRNA of this limited set. Thus AA^{U}_{C} will code unambiguously for asn. The other three sets of codons will be read with varying degrees of ambiguity depending on how much wobble can occur in each position. Thus, because of wobble, the presumed anticodon loop for serine

3′ UG*UCG*UU

will read not only the codons AG^{U}_{C} but also, with less affinity, the codons GG^{U}_{C}, and thus occasionally insert serine by error into a glycine position.

These ideas should not be pressed too far. Our discussion is naive since we have made no allowance for G ≡ C pairs being stronger than A = U pairs, nor for stability being affected by stacking effects depending on base sequence. Further experiments are needed to allow correctly for these and other effects.

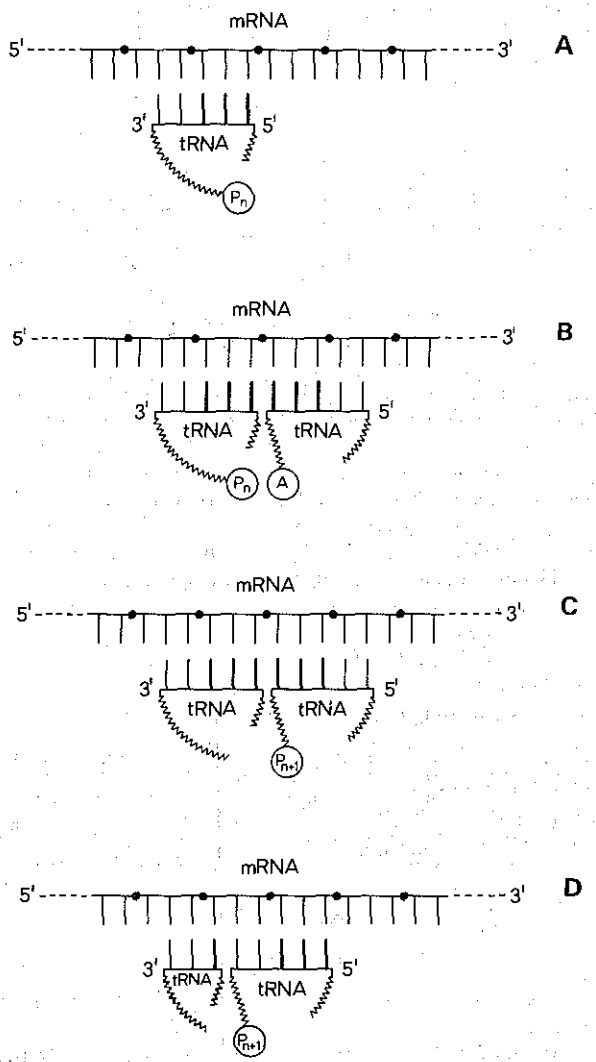


Fig. 2. Each vertical line represents a base. The dots on the messenger RNA show the phase in which it should be read. The representation of the tRNA molecules has been greatly oversimplified. (A) The tRNA in the FH configuration with the nascent polypeptide, P_n, attached, sits on the mRNA making five base-pairs. (B) The tRNA carrying the next amino acid, A, goes onto the mRNA in the hf configuration, also making five base-pairs. (C) The polypeptide chain is transferred to the amino acid to give the polypeptide P_{n+1}. (D) The tRNA carrying the nascent peptide flips to the FH configuration. The tRNA which has given up its amino acid is now held by only three base-pairs so that it will shortly fall off, giving a situation similar to that of Figure 2A but moved along three bases. These figures are purely explanatory and show neither the correct scale nor the relative orientations of the components.

been made into an ingenious game by Eigen (1973). It is thus plausible to consider that in the primitive soup molecules existed not unlike the present tRNA molecules (though naturally without modified bases) many duplicate copies of which were produced from a nucleic acid template by some unspecified primitive copying mechanism.

3. General Requirements

There are a number of general requirements for a primitive system of protein synthesis. These are all aimed to reduce gross errors in the process while not necessarily removing minor errors. For example, the message must be read fairly consistently in the same phase since if the phase slips too often during the reading the resultant polypeptide will differ too much from the ideal one without any errors. On the other hand an occasional incorrect amino acid will not necessarily be unacceptable.

It seems likely that one such requirement is that, at any moment, the particular tRNA molecule to which the growing polypeptide chain is attached is bound to the messenger RNA by sufficiently strong bonds such that the two will not usually come apart until the polypeptide chain is transferred to the amino acid attached to the next tRNA. Otherwise polypeptide synthesis would be repeatedly interrupted and, worse, would usually resume again at the wrong place in the message.

The tRNA attached to an incoming amino acid, on the other hand, need not be bound to the messenger RNA so strongly and could perhaps come off and go on again before receiving the polypeptide chain since this would only slow the process rather than make a gross error in it. A tRNA with no amino acid attached should bind rather weakly, if at all, so that it will not interfere too much with the synthetic process.

It is possible to devise several rather involved schemes whereby each primitive tRNA was bound to the primitive messenger RNA by only the three bases of the anticodon. Since such an attachment by itself is unlikely to be stable one must invoke complicated interactions between tRNA molecules, adjacent on the message, in order to get a stable complex and in order that the message be read systematically in one direction. We shall not consider such schemes further here but will instead explore schemes in which the tRNA holding the polypeptide chain is held by 5 rather than by 3 base pairs.

4. Theoretical Assumptions

Our idea contains three main elements:

(1) That under the conditions then existing of temperature, salt, etc a tRNA molecule making *five* base pairs with a messenger RNA (rather than the present three) is stably attached for a sufficiently long time.

(2) That the anticodon loop of each primitive tRNA could take up two configurations. In the first of these (called by Woese (1970) the FH configuration because it was originally proposed by Fuller and Hodgson (1967)) the five bases at the 3′ end of the seven base anticodon loop are stacked on top of each other. In

infectious DNA recombinant molecule should a laboratory accident occur.

Our first witness this morning is Dr. George Pieczenik from Rutgers University. I am going to call upon Mr. Hollenbeck, the ranking minority member of this subcommittee, and Representative from New Jersey, for the purpose of making the introduction.

Mr. HOLLENBECK. Thank you, Mr. Chairman. Today and in the past there has been concern in the public about this issue. As we begin our second phase of hearings today on the science policy implications of this area of genetic engineering, our study is going to be expanded to include, I hope, relevant testimony concerning evolution and epidemiology, subjects which have not been widely discussed before us until now.

In this regard, I am very pleased to have the opportunity to introduce our first witness, Dr. George Pieczenik. He is a scientist at Rutgers University, the State University of New Jersey. He has recently jogged the scientific community with a researched and published theory which questioned and challenged the entire basis for the current concerns over recombinant DNA research and genetic engineering.

He has worked at the Cambridge Laboratory of Molecular Biology for the past 6 years with such scientists as Francis Crick and Sidney Brenner. Recently his position has been presented in the Journal of the Origin of Life, and he has received recognition for that in several science publications and other publications such as Time magazine.

[The article referred to follows:]

Food and Drug Administration regulations for the sale of any biologic material. FDA has current authority to inspect that material and make sure it is what it's supposed to be before it's sold in the marketplace.

Mr. BROWN. So there is a possibility—although we have many cases of commercial exploitation—that there would be a minimum of hazard, of introducing a recombinant DNA molecule into the environment, assuming that our purification processes were adequate?

Dr. TALBOT. Assuming the purification process was adequate, the only problem will be an accidental release of that organism into the environment, just as in laboratory experimentation.

This would not be a case where the company would want to deliberately release the organism into the environment. They would want to separate the insulin and release that.

Mr. BROWN. Well, I'm interested in this because I think much of our thinking has been shaped by consideration of a situation in which the actual recombinant molecule needed to be released into the environment in order to achieve the goal.

For example, the nitrogen fixation situation would be in that class. And maybe there are others. I have no idea really. But these classes pose two substantially different kinds of hazard questions to the public.

Dr. TALBOT. Absolutely.

Mr. BROWN. The question I was going to raise is, what degree of precaution would be necessary to be sure that a recombinant DNA molecule contained in a bacteria or any other substance, once released to the environment, posed no hazard to the biosphere?

Dr. TALBOT. Well, the current NIH guidelines prohibit the deliberate release into the environment of any organism containing recombinant DNA molecules.

Mr. BROWN. Right. But I'm posing the question in terms of future commercial development which requires that this be done.

What processes would be necessary to insure safety? Have we investigated this problem—because this is a much more complex problem than merely insuring laboratory safety?

Dr. WHELAN. They've not been examined, and one can think of good examples, in addition to the nitrogen-fixing gene.

I should say, before I forget, by the way, that insulin as synthesized in the recombinant DNA scenario would be different from present commercial insulin, because surely it would be human insulin that would be chosen for synthesis. Presently we rely on beef insulin, which has a somewhat different structure from the human product. So, to that extent, it would be an improvement.

But one could think of food proteins, single-cell protein, for which there's a great need. I don't see how you could avoid distributing the organism. You might be using the whole organism as the source of protein, because you could presumably engineer an organism which had the minimum nucleic acid which is undesirable in that type of product and the maximum of protein with the maximum of the essential amino acids.

But there's a whole range of products where as long as the containment facilities were good, there would be no disposal of the recombinant DNA molecules. Part of the pressure that's coming from industry is due to the fact that they see very well—and have for many

should be extraordinarily careful about releasing the products of these experiments.

On the other hand, I wouldn't like to be challenged too much on this one, but if one of the hoped-for examples were to come about, namely that insulin could be synthesized by a bacterium, and the bacterium was one that was so crippled that its survival outside the manufacturing organization was virtually impossible, then I would say there's a good practical example. But that's conjecture.

It's very difficult to look more than a year ahead.

Chairman THORNTON. I think that's a very responsive answer. It would depend entirely upon what the research showed.

You are suggesting that if research efforts were successful in developing insulin, with a very weakened bacteriological agent producing the insulin, this might be the kind of thing that should have an early release?

Dr. WHELAN. Yes.

Chairman THORNTON. I assume that nitrogen-fixing bacteria for agricultural uses might be another example.

I have a great deal of difficulty in knowing what part of the dispute is really conjectural and what research is presently being conducted in the research facilities.

We were told on Tuesday that the chromosome of a fish stretched out might be 1 meter in length. You know, that's an awfully long stretch of genetic information to be compressed in one cell.

And if I understand the nature of the recombination efforts that are now proceeding, you're splicing just a very select set of gene information, which might be just a fragment of that long pattern that consists of the instructions for building a fish. You're dealing with just one little fragment of that, and putting it into a bacteria.

Is that the present level of recombination activities? Can someone help me on that?

Dr. GARTLAND. Yes, Mr. Chairman, in general that is the type of experiment that is being conducted right now. Taking your example, it would be taking a bit of the DNA out of that 1 meter of fish chromosome DNA and putting it into a much simpler system, such as E. coli, where one would be able to study that gene, and perhaps how it functions, in a much simpler genetic background, which is the type of experiment which would be very difficult, if not impossible, to do on a whole fish.

Chairman THORNTON. And the E. coli with the fragment of that gene information implanted does not become a fish?

Dr. GARTLAND. No, it does not become a fish. But this is the whole crux of the controversy, namely can one convey to that E. coli any properties that could cause ecological damage.

Dr. TALBOT. The E. coli has a few thousand genes, and at the most you're putting in one or two genes, in this instance fish genes. You still have 99.9 percent E. coli and 0.1 percent added DNA, so you don't have a fish; you have an E. coli which contains a little bit of fish DNA.

Chairman THORNTON. Now, except for the fact that this is manipulated—and the word "manipulated" has the word "man" in it, that it is man-caused, is this something similar to what happens when an E. coli gene has a mutation that alters that structure somewhat? Of course that mutation may not be an addition of a particular gene;

As you know, the proposed risk assessment experiment by Dr. Rowe at NIH has aroused some local concern. It's a P4 risk experiment.

I would like to ask, with regard to your statement, where those organizations are, and who are the individuals or organizations that are evaluating this kind of risk assessment?

Dr. WHELAN. The principal one that I have in mind is the European Molecular Biology Organization Committee on Recombinant DNA Research. We're in close touch with them, because the Secretary General of ICSU, who is Sir John Kendrew, is the director of the EMBO Laboratory in Heidelberg.

They are constructing a P4 facility there, and that is one possible site for some of the experimentation.

Chairman THORNTON. Can you tell me what kind of experimentation is proposed?

Dr. WHELAN. They've discussed several. I think my colleagues here might be more knowledgeable, because they've recently been in touch with EMBO to share information.

Chairman THORNTON. Do we have a volunteer to expand further on this question?

Dr. GARTLAND. Yes, Mr. Chairman.

I can't speak specifically of the experiments which EMBO is proposing to conduct, particularly at their facility at Heidelberg, but in this country the NIH is planning to sponsor within the next several months a symposium on this whole question of risk-evaluation studies.

I think there's going to be quite a bit of discussion as to what kinds of experiments ought to be done to assess the risks. It probably does not make much sense for people to be going off in different directions, doing different kinds of experiments, if there is not a consensus that when you get the answers that people are going to agree that they were well-designed experiments that provided useful answers.

So the approach the NIH is taking, with the exception of one experiment that Dr. Rowe is doing, is to have this workshop. And we are going to get input into that workshop from WHO, which has been conducting a survey as to what types of experiments different scientists in Europe think ought to be done.

Dr. WHELAN. I could give you, Mr. Chairman, for the record written statements of the experiments that are proposed, taken from the minutes of the EMBO meeting, and also our own COGENE-planned experiments.

Chairman THORNTON. We will be pleased to receive those additions to your testimony, if you will submit them.

Without objection, they will be received for the record.

Chairman THORNTON. Dr. Gartland, Dr. Wald testified earlier this week that industry had shifted its position with regard to the guidelines.

Are you in a position to evaluate whether such a shift occurred, or did you perceive such a shift in position?

Dr. GARTLAND. No; I'm not really in a position to comment on that. I have not perceived any great shift.

One of the problems is that industry in this country, specifically with the recombinant DNA problem, has difficulty speaking with a

Chairman THORNTON. We were reminded at an earlier set of hearings that Mark Twain not only had comments about being talked to death, but commented that Wagner's music was not as bad as it sounded. [Laughter.]

I wonder if we may be faced with that same kind of problem in connection with the area in which are dealing. There are serious problems to be considered, which require application of our best abilities to think and to study and to evaluate the problems, not only as they relate to one particular section, area, or city, but to all nations of the world. We do thank you for your presentation.

Do you have further comment with regard to that?

Dr. WHELAN. I think that a realization of the global nature of the problem is coming, and I'm very encouraged by what I've heard in this morning's testimony from Dr. Fredrickson. I know that they're very anxious to take action at the international level. They have funds, and we hope to work with them.

But I do wish that the temperature might drop a little, and I think there's a good deal more fever in the United States than one sees elsewhere. The mood elsewhere is calmer. It is a question of taking practical action to determine what are the risks, because one can go on debating forever—and the analogy Dr. Fredrickson used about the railway trains in Kansas is a good one. And it's time to determine what are the risks, and hopefully remove some of the fears that people have raised.

Chairman THORNTON. Thank you very much.

Mr. Brown?

Mr. BROWN. Dr. Whelan, I appreciate your statement. I think that there has been a tendency to give insufficient emphasis to the international aspects of this problem, and you help us to focus on that.

You interjected a comment in your statement that we did not need a crash program in this research, but a period of long and careful development. The question that that raises is, how do we in this country particularly, where there is substantial private sector interest, as well as Government interest, bring about a carefully planned program of long and careful development instead of a crash program?

I'm thinking here of a situation where a private research organization sees a promising commercial development and wants, and has the capability, to devote substantial resources to it. And then of course for commercial reasons they don't want to reveal precisely what they're doing, and they make a breakthrough and they want to reap the benefits of this breakthrough.

What tools do we have available, in comparison to the more-controlled economies, to bring this into a pattern of long and careful development instead of the possibility of sudden and rather dramatic spurt in a particular—and possibly very narrow—area, but still an important area?

Dr. WHELAN. I am very sympathetic to industry's problems, and I hope that their problems can be solved. If there are practical benefits from this research, one would like to see them put into practice.

What I meant in saying that I don't agree that a crash program is needed is that if one introduces legislation too hastily, legislation which doesn't have sufficient flexibility, this may hamper the possible development of the practical benefits of this kind of research. It may also hamper the progress of research in laboratories.

List of Annexes

1. (a) European Responses to the Recombinant DNA Debate
United Kingdom, France, The Netherlands, West Germany, Scandinavia, other West European countries (Switzerland, Italy, Ireland), Eastern Europe
(b) Initiatives at the European Level
EMBO Standing Advisory Committee, European Science Foundation, U.S. Guidelines in Europe, Future developments in Europe

J. Tooze

2. Report on the Activities of the Committee on Safety in Recombinant DNA Research, Federal Republic of Germany

H.G. Zachau

3. Reports of Activities Displayed in Japan in Relation to Recombinant DNA Research

Y. Tazima

4. Report on the Activities of the NIH Recombinant DNA Molecular Program Advisory Committee, U.S.A.

R. Curtiss, III

5. The WHO Special Programme on Safety Measures in Microbiology

K. Bögel

6. The Activity of the Commission for Experimental Genetics of the Swiss Academy of Medical Sciences

W. Arber

Copies of the annexes are available to members of the ICSU General Committee and General Assembly on application to Mr. F.W.G. Baker, ICSU Secretariat, 51 Boulevard de Montmorency, Paris, France 75016.

that an attempt should be made to require that original papers published in scientific journals contain an indication of the containment facilities used.

M.F. Singer gave an account of the events which had taken place recently in Cambridge, Massachusetts in relation to an application for the reconstruction of a series of laboratories at Harvard University to provide a P3 facility. She explained the need for scientists to be aware of such problems and to take appropriate acion to ensure that the public were better informed about the work being done and of the risks, if any, involved.

U.S.S.R.

G.P. Georgiev stated that there is at present no state or scientific committee for the regulation of experiments. There is a national committee forming under the chairmanship of A.A. Bayev with representatives of science, medical science, and of the Ministry of Health. It can be expected that the NIH guidelines will be followed. Some work would be carried out on mammalian genes under P3 and P4 conditions. A P4 facility was being constructed in his institute.

He suggested that it would be useful to have one global committee, so as to provide one set of international guidelines.

W.H.O.

K. Bögel said that the WHO Sub-Committee on Safety in the Handling of Microorganisms and Cells employed in Research had a major global responsibility, but was not concerned with technical detail. Information on benefits and risks would be collected, synthesized and disseminated; the Organization has a special duty to inform developing countries (see Annex 5).

There would be an expert group to advise WHO continuously on all international aspects of laboratory safety and emergency services. A consultation would also provide information on the benefits and applications of recombinant DNA research in medical sciences.

He suggested that a number of fields relating to tropical parasitic diseases had been neglected. He drew attention to some of the areas in which there might be some overlapping between WHO and an ICSU group if formed.

Switzerland

W. Arber (Annex 6) explained that the freedom of scientific research was maintained in the hands of scientists who made the decisions with regard to the degree of risk and type of experiments allowable. In general the draft NIH guidelines were followed. He indicated, however, that there were some problems with respect to the industrial research using recombinant DNA.

France

E. Wollman summarized the situation in France (see Annex 1). Two committees have been formed, one moral-ethical, the other a technical control commission. All research done in the recombinant DNA field is submitted to the latter commission which uses the draft NIH guidelines. Research grants will not be allocated until after the proposed research has been submitted to the commission which defines the safety conditions under which it should be conducted. Both the project leader and the head of the academic institution in which the research is carried out have to agree to follow the recommendations of the commission. A local safety committee ensures

1. Reports on Activities of Other Organizations Studying Recombinant DNA

European Molecular Biology Organization (EMBO)

J. Tooze reviewed the situation in EMBO, which has a Standing Advisory Committee on Recombinant DNA. This provides technical advice to research councils, national groups, institutes, etc. The Committee will meet to reconsider the NIH guidelines and the report of the (U.K.) Williams Committee. As an interim measure the EMBO Committee has recommended that the NIH draft guidelines be adopted.

The Committee intends to establish a voluntary registry of recombinant DNA research in Europe.

J. Tooze had summarized the situation for EMBO and of other European committes in Annex 1.

European Science Foundation (ESF)

J. Tooze explained that the ESF provides a forum for research councils and academies from 17 European countries. It has established an *ad hoc* Committee on Genetic Manipulation with the tasks of surveying European initiatives relating to recombinant DNA research and considering the scientific, social, legal and philosophical implications of this research, so as to facilitate the development of a common European attitude. This *ad hoc* Committee cooperated closely with the EMBO Committee, and had also suggested as an interim measure the adoption of the draft NIH Guidelines.

In response to a question as to what ICSU might do that was not being done already, J.C. Kendrew suggested it could provide a useful function in (i) evaluating guidelines and preparing a set of principles for workers in this field; (ii) assisting in ensuring the availability of suitable strains and materials; and (iii) helping in the provision of training, especially to scientists from developing countries.

Federal Republic of Germany

H. G. Zachau indicated that the Deutsche Forschungsgemeinschaft was the main agency concerned in the BRD. There is a Commission which includes in its membership scientists from various biological disciplines and, as guests, representatives from ministries, industry and the lay public. For the time being no legislation is being prepared. He provided a written report (Annex 2). About 40 questionnaires had been returned for the preparation of a registry. The next meeting on 13 July would consider among other things, the NIH guidelines. There is however a Law on Contagious Diseases which might provide cover for some types of experiment.Projects would only be funded if the guidelines were adhered to. He expressed some concern about the duplication, even triplication - of some of the initiatives and suggested that if ICSU created a committee it should be a global technical committee and leave general questions to other national and regional groups.

J. Tooze drew attention to an application in Germany by a British company for a patent involving recombinant DNA. There was a discussion on the question of the patenting of the results of research on recombinant DNA. This showed that patents had been applied for in several countries. M. Singer explained that some universities in the U.S.A. take out patents to ensure either that the subject of the patent can be used freely or that the money from patent rights can be utilized for worthwhile causes.

Information Services

This would require the recruitment in whole or in part of the services of a qualified scientist and a secretary. Their salaries plus the costs of collecting, maintaining and distributing information are estimated to be: $ 50,000

Technical Services

(a) Maintenance of a strain collection, including materials, handling, part-time assistance, the cost of distributing strains, plus a $ 2,000 investment in equipment in the first year would cost: $ 18,000

(b) Support of the cloning experiments $ 15,000 - 20,000

Training and Education

The annual budget would provide for one 3-week training course for 20 students, fellowships for 5 trainees to attend courses and two 3-week lecture tours: $ 75,000

Total annual budget $ 167,000 - $ 172,000

(b) *Evaluation of hazards*

The hazards are at present conjectural and more information is needed to evaluate them. It is therefore important to stimulate investigation of the possible existence and extent of such hazards and to distribute information relevant to the revision of guidelines for the safe performance of this research.

(c) *Ethical and legal issues*

This research has evoked discussions on various legal and ethical issues. Information on such debates occuring in one place should be disseminated because of the possible relevance to discussions of similar issues in other areas of the world.

(d) *Physical, chemical and biological containment for safe conduct of experiments*

Information on guidelines and containment procedures should be made available to the scientific community for the uniformly safe conduct of this research.

(e) *Sources of technical advice, equipment and materials*

Research on recombinant DNA molecules is a rapidly changing area of scientific investigation with opportunities for development of new technologies. Information on sources of technical advice, equipment, enzymes, host-vector systems etc. should be made available through a central archive.

(f) *Laboratories engaged in research on recombinant DNA molecules*

A world-wide registry should be established of laboratories engaged in this research, indicating the nature of the experiments being conducted and the number of individuals engaged.

(g) *Publication of research*

The Committee should encourage the inclusion, in all publications dealing with recombinant DNA, of a description of the physical, chemical and biological containment procedures practised, to aid and assist others who might consider repeating the work.

A Proposal to Constitute a Scientific Committee on Recombinant DNA Research (SCORD)

I. PURPOSES AND OBJECTIVES

SCORD shall be a Scientific Committee of ICSU established for the following purposes:

a) to serve as a non-governmental, interdisciplinary and international council of scientists and as a non-governmental source of advice for the benefit of governments, governmental agencies, scientific groups and individuals, in respect of research on recombinant DNA, the practical benefits that may be derived therefrom and the need for such research to proceed under appropriate and generally agreed safeguards.

b) to assemble, review and generally make available information on safeguards, containment facilities and other technical matters.

c) to foster opportunities for the training of and international scientific exchange between workers in the field.

d) to make itself available as a medium through which the many national, regional and other international bodies with interests in recombinant DNA molecules may communicate.

e) to take note of the widespread concern over the possible deliberate or inadvertent dispersal of agents constructed by recombinant DNA techniques, to be vigilant regarding such possibilities and to attempt to foster public discussion of these situations should they arise.

II. MEMBERSHIP

The composition of SCORD should be as follows:

(a) One representative designated by each international union federated in ICSU which desires to participate in the work of The Committee.

(b) Further members shall be appointed by the General Assembly in order

functions under the direction of the newly introduced DNA.

In the field of medicine this new technology opens up the possibility of dealing effectively with genetic disease, and of using bacteria to synthesise molecules of medical importance, for example human hormones and antibodies. In agriculture we see the possibility of transferring to crop plants the genes of micro-organisms which cause the fixation of nitrogen. In industry we see the possibility of creating microorganisms specifically designed to synthesise food protein, and other important natural products.

The concern stems from the fact that at present we are not able to predict in detail the behavior of new forms of life which are essentially hybrids between species that do not normally exchange genetic information. This concern, shared by the molecular biologists themselves, led to a self-imposed limitation on the exploitation of these new genetic techniques, while guidelines were drafted to regulate the safety conditions under which this work should proceed.

The concern, which was first expressed in the U.S., was also shared by scientists throughout the world. Numerous national, regional and international committees have been established to monitor and control the conduct of this research. Because of the global implications of recombinant DNA research it seemed appropriate that ICSU should examine what role, if any, it should play. A meeting of experts was convened at Schloss Laxenburg by the ICSU Executive Board and it recommended the establishment of an *ad hoc* committee to carry out a study and to report. The General Committee endorsed this proposal and the ICSU *ad hoc* Committee on Recombinant DNA Molecules was established on 20 September 1975 under the chairmanship of W.J. Whelan (U.S.A.). The Bio-Unions and other bodies were asked to recommend persons to serve on the Committee and the other members appointed by President Brown were:

W. Arber (Switzerland)
F.W.G. Baker (ex-officio)
R. Curtiss (U.S.A.)
G.P. Georgiev (U.S.S.R.)
J.C. Kendrew (ex-officio)
K. Murray (U.K.)
E. Reich (U.S.A.)
M.F. Singer (U.S.A.)
Y. Tazima (Japan)
J. Tooze (B.R.D., Secretary)
E. Wollman (France)
H.G. Zachau (B.R.D.)

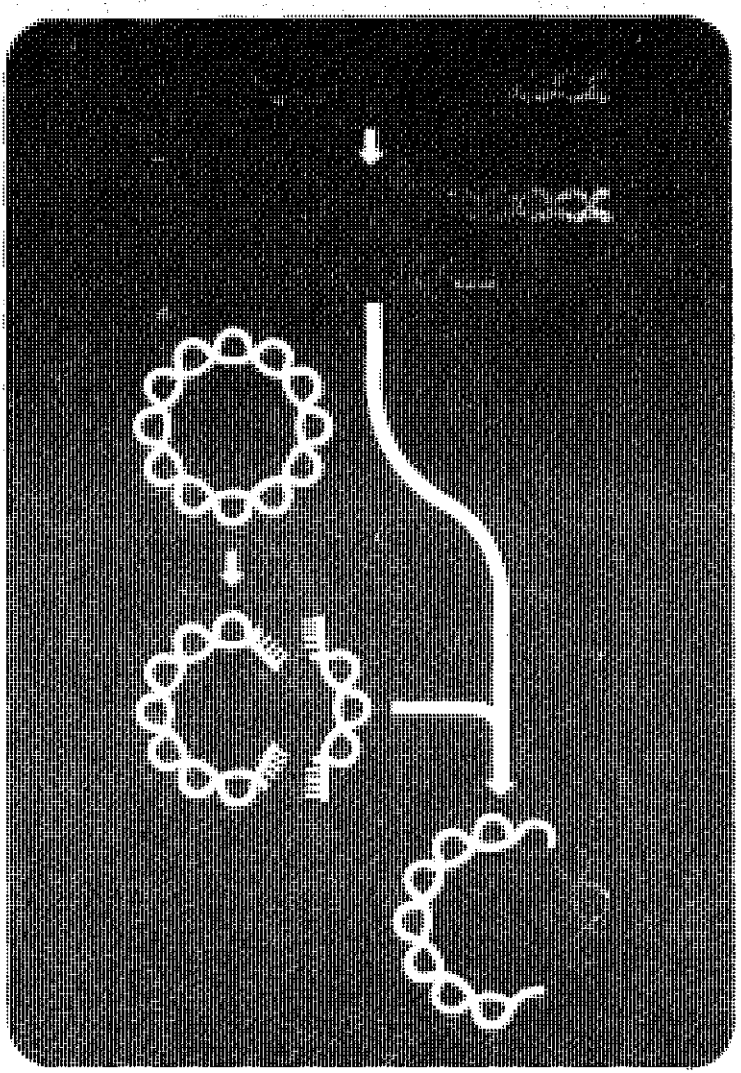
In addition the *International Cell Research Organization* appointed C. de Duve as an observer and the *World Health Organization* sent K. Bögel as an observer. C. de Duve was the only person unable to attend the *ad hoc* Committee Meeting.

The *terms of reference* of the *ad hoc* Committee were to study and advise on the following aspects of research on recombinant DNA:

(a) to observe the development of public opinions and governmental actions in relation to research on recombinant DNA. To serve as a support to national and regional scientific groups in their efforts to ensure the drafting of appropriate guidelines for research in this area. This may initially be largely a "watching brief", depending very much on future developments in individual countries and areas. It is hoped that these developments will provide favourable precedents, but if not, there might be a need for strong and authoritative representation at the highest possible level.

(b) to collect information and to act as a central source of information on the following topics:

INTERNATIONAL COUNCIL OF SCIENTIFIC UNIONS



REPORT OF THE *ad hoc* COMMITTEE ON RECOMBINANT DNA MOLECULES

international scene; if others will do them, or if we can catalyze others to do them, we'll certainly be happy. We have no wish to try to take on everything.

But, first of all, in talking about the things that we'd like to see done, given our premise that the research should continue, we would like to help secure universal agreement to safety guidelines and to assist in securing harmonization of guidelines so that there might emerge an international code of practice, not so compromised by individual exceptions as to become a set of pious hopes.

We hope to act to link and bring together the many national and regional bodies acting in the field, and be a means through which they can communicate. We see also a clear and pressing need for good training in safety measures to be available wherever the research might be carried out, and we hope to work with the World Health Organization to this end.

We also see a need for the wide availability of good training in the technology itself, not just in North America and Western Europe, and we will work with UNESCO and other bodies to this end.

I go along with Mark Twain that it's a terrible death to be talked to death. I feel we have to move away from the present situation where the main tools of debate are guesswork, intuition, prejudice, and conjecture. We see the need to conduct risk-testing experiments, designed to examine the reality or otherwise of some of the alleged hazards.

We are in touch with organizations which are already planning such experiments and we have our own panel of experts now planning experimental protocols, for experiments which are not presently planned by other bodies.

We also see the need for a thorough examination of the ways in which industry might use this technology on a large scale, with safety and with due respect for industry's need to protect its discoveries. I hope that COGENE will succeed quite soon in organizing a discussion meeting in a representative international context. I already have a potential financial sponsor and a potential national academy to act as a host.

My own input into your deliberations then is to express the hope that actions be generated at the international level, a relatively neglected aspect, I think, of the debate on recombinant DNA. I am personally convinced of the need in the United States for Federal legislation that will give the NIH guidelines the force of law in all laboratories and that there should be adequate public disclosure and public scrutiny of the details of planned and ongoing research.

I hope that the legislators will be sufficiently enlightened to build flexibility into the regulations so that these may be changed with the advent of new knowledge.

In this regard I'd like to refer to the admirable report prepared for you by Dr. McCullough. Looking there at a quotation from Dr. John Platt, I'd like to take exception to this comment, because he seems to be calling for a crash program to provide solutions to some of the problems. He uses the analogy for the need in World War II for improved antisubmarine warfare.

I happen to have worked in that program in World War II, and I think the analogy is wrong. Recombinant DNA research may trans-

Nevertheless, the keen interest of so many of the member unions of ICSU in recombinant DNA, and the proven effectiveness of ICSU in coordinating scientific activities on a worldwide basis prompted, first of all, a study to recommend or not recommend whether a committee should be created. I was the chairman of that ad hoc group.

I would like to submit for the record, Mr. Thornton, a copy of the report of that group that proposed the formation.

Chairman THORNTON. Yes, we have that printed report as part of the material which has been submitted to us, and we will receive it for possible inclusion in the report of these hearings, without objection.

Dr. WHELAN. Thank you.

It also refers to annexes, which are rather bulky, but which are available, that to provide a very thorough study of the state of the technology and governmental actions around the world as of the middle of 1976.

Despite, as I have already referred to, the many committees already in existence, this study group felt that there was a need for a truly international, interdisciplinary, nongovernmental, and apolitical body that would help to solve some of the problems and would take appropriate initiatives.

This recommendation was accepted, and when it was accepted the general assembly of ICSU deliberately widened the terms of reference of the committee to include genetic experimentation in general, not just recombinant DNA research, taking the line that we are interested in genetic experimentation in general. Often the different technologies are simply means to a common end, and there would be little point in having a committee, a separate committee, for each branch of genetic manipulation. We begin with one committee which has wider terms of reference, but certainly will initially concentrate on the recombinant DNA aspect.

The members of COGENE come from the major nations involved in recombinant DNA research and include representatives of seven of the member unions of ICSU that have a close interest in the results and applications of the research. Individuals who are members of the committee include: Paul Berg, whose name is well known to you; and someone who was also mentioned this morning, academician Alexander Bayev, who is the chairman of the Soviet Committee on Recombinant DNA Research.

The potential usefulness on the international scene of this new nongovernmental committee is attested to by the fact that UNESCO, FAO, and WHO have appointeed observers to attend the meetings of COGENE, with the possibility of giving financial support to some of the activities that we have in mind.

In creating this committee, ICSU did not have it in mind to preside over the banning of research on recombinant DNA. Rather, ICSU wishes to see the research proceed, recognizing at the same time the widespread concern at the potential hazards, and the complex moral, legal, and ethical issues for society that have been opened up by this new field of scientific endeavor.

I referred to the fact that I, myself, have not engaged in the research, but I hope I can help your scrutiny of the issue and, without being redundant, if I pass on some information about what we hope to do, making those remarks in the context of the impressions that I

Is that correct?

Dr. FREDRICKSON. We are cognizant of that, and we certainly want to present every opportunity for their involvement, and we will.

Chairman THORNTON. Especially with regard to this Program Advisory Committee, which is in the process of now revising the guidelines. The public is involved in that, is that correct, sir?

Dr. FREDRICKSON. The Director's Advisory Committee meetings are always open to the public. The meetings of The Technical Recombinant Advisory Committee are also public.

Chairman THORNTON. Any questions, Mr. Dornan?

Mr. DORNAN. No questions, Mr. Chairman.

Chairman THORNTON. I'm going to invite Mr. Wydler, if you have any questions——

Mr. WYDLER. I have no questions, Mr. Chairman. I appreciate it.

Chairman THORNTON. Mr. Yeager?

Mr. YEAGER. Just one, Mr. Chairman.

May we have permission to request some further information for the record?

Chairman THORNTON. I will ask, Dr. Fredrickson, if you would be willing to respond to such written questions as we may submit?

Dr. FREDRICKSON. Most gladly. I'd be pleased.

Chairman THORNTON. In recognition of your schedule, we would like to invite you to continue to remain onboard if you can do so, but if your requirements are otherwise we will now proceed to the next witness, Dr. W. J. Whelan. Perhaps your other companions may remain if it is necessary for you to leave.

Dr. FREDRICKSON. Thank you, Mr. Chairman. I regret that I do have to go.

Chairman THORNTON. May I then express, on behalf of our subcommittee, our deep appreciation to you for your fine presentation and your responsive answers to our questions. Thank you, Dr. Fredrickson.

Dr. FREDRICKSON. Thank you, Mr. Chairman.

Chairman THORNTON. Our next witness is Dr. William J. Whelan, chairman of the department of biochemistry, University of Miami School of Medicine. Dr. Whelan helped to organize a very successful symposium in January of this year, which was cosponsored by that university and the Cancer Research Institute on the topic of molecular cloning of DNA and genetic manipulation as it affects the cancer problem.

We've asked Dr. Whelan to appear today, since he also serves as the chairman of the Committee on Genetic Experimentation, a scientific committee established by the International Council of Scientific Unions.

We hope, Dr. Whelan, that you'll be able to provide us with information on foreign nations' considerations of the DNA recombinant molecule research issue. We appreciate very much your attendance.

You may proceed.

[A biographical sketch of Dr. Whelan follows:]

DR. WILLIAM WHELAN

William Joseph Whelan, Ph. D., D. Sc., 52 years old, Professor and Chairman, Department of Biochemistry, University of Miami School of Medicine, Miami, Fla. Dr. Whelan is the General Secretary of the International Union of Bio-

Could you give us just a quick answer to that, and maybe we could follow it up in more detail in some other way?

Dr. FREDRICKSON. I believe that is absolutely essential. The NIH guidelines, which, under the proposed legislation would be promulgated as the preliminary or initial standards, contain a prohibition against the deliberate release of any recombinant product into the environment at this time.

Clearly the time will come in agriculture, if it works there—and undoubtedly in other aspects of industry—when the decision point will have to be crossed, when do you release? And we're going to need an extraordinary amount of wisdom in developing criteria which will determine whether that should be done or not. It is not too soon to begin to worry about how that form of regulation is actually going to be handled.

Mr. BROWN. Thank you, Mr. Chairman.

Chairman THORNTON. Thank you, Mr. Brown.

Mr. Hollenbeck?

Mr. HOLLENBECK. Thank you, Mr. Chairman.

Dr. Fredrickson, on the subject of guidelines, certain groups have claimed that the development of your guidelines represents a conflict of interest on the part of some of the scientists involved in the drafting because those same scientists may be later conducting the research.

Can you address yourself to that accusation?

Dr. FREDRICKSON. A portion of the scientist members on the technical committee that put these guidelines together are actually engaged in molecular biology; some are not.

The content and substance of the guidelines is so extraordinarily technical that it would be absolutely impossible not to have experts who are engaged in the work themselves primarily concerned with the development of the guidelines.

I think that our obligation is that the rest of us, who are in a sense all lay people—even though we may have scientific backgrounds—but lay people in this area of molecular biology, must take great care that our opinions are as well informed as possible. There should be opportunities for the public to have a view of the people who put the guidelines together, because if we don't understand the substance, we can very often judge those that put them together and the sincerity of their determination to protect a broader interest than their own.

It was on this basis that we had a hearing, a widely announced public hearing, at the time these guidelines came forward. And it is why we have responded carefully to a whole range of comments.

I think that from the beginning, we have engaged the public in the opportunity to know the full basis of the construction of these guidelines.

As you may know, the NIH took care to publish in this thick yellow book [indicating] the complete hearing record of that public hearing in February 1976, and all letters to me thereafter concerning the nature of the guidelines. And we shall do the same with the succeeding documents, so that there is available to all people, regardless of what they think, a clear understanding of what was the nature of the input on which these decisions were based.

develop some of these scenarios, purely as a means of stimulating further thinking about this matter.

Dr. FREDRICKSON. Indeed, I agree with you, Mr. Brown. We have engaged in that privately. We have refrained and resisted the temptation to put too many of them into environmental impact statements, simply because we have no way of assigning any probability to those scenarios.

But we hope that we can begin to develop a basis for doing that as this information unfolds.

Mr. BROWN. This committee is really not so much concerned with the regulation of recombinant DNA research as it is with the broader science policy issues involved. That is the reason for my question.

Dr. FREDRICKSON. Yes.

Mr. BROWN. And, frankly, I don't know how we get at these issues except to pursue some rather simple procedures of using all of the knowledge that we have and the best minds that we have, to avoid as many future accidents, as well as present laboratory accidents, that we can.

Dr. FREDRICKSON. I am quite sympathetic to the committee's position in this regard.

Mr. BROWN. Thank you.

Chairman THORNTON. Thank you very much, Mr. Brown.

I do understand that during the past Congress a group of 25 or 30 Congressmen did petition the Office of Technology Assessment for an assessment of the kind that has been described. I don't think that that work has progressed to the point of expressing any conclusions. In fact, if I understand correctly, that they are still trying to decide exactly what issues they can address in that group.

Are you familiar with the OTA assessment procedure at all, Dr. Fredrickson?

Dr. FREDRICKSON. I'm quite familiar with OTA Mr. Thornton.

Chairman THORNTON. Are you familiar with this petition?

Dr. FREDRICKSON. I'm not familiar with whether they are investigating this particular issue.

Chairman THORNTON. Mr. Yeager?

Mr. YEAGER. I think they are in the situation, Mr. Chairman, where, as you mentioned, are simply trying to develop a proposal that would make some sense of the areas in which they might conceivably make a contribution. But that has not been developed to the point where it has been brought before the Technology Assessment Board for the Board to discuss, as to whether they should or should not do it.

Chairman THORTON. Thank you.

I would like, if I may, before recognizing Mr. Hollenbeck for questions, to accept one quotation which is in the prepared statement which you have submitted, and to call for such additional comment as may be appropriate with regard to that. This quotation is from the interim report transmitted to HEW Secretary Califano on March 15.

The Secretary in releasing the report on March 16th stated that, and I quote:

> 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:

This week "60 Minutes" had an example of a plant in Texas where, if there were not deaths, there were severe illnesses. The Kepone situation is an example.

Is there a difference in kind between the hazards reflected by this kind of research and the hazards reflected by recombinant DNA research?

Dr. FREDRICKSON. I suspect that the kind of definition you are using, Mr. Brown, by that there are not great differences.

You ask the question in terms of "Can as much harm be done by the introduction of a chemical, a single chemical, into the environment as might be done by recombinant DNA techniques?" It is my informed guess and a value judgment that the introduction of some chemicals might be much more harmful or widespread in their effect.

Mr. BROWN. What causes the difference in our attitude toward recombinant DNA and chemical R. & D.?

Or is there a difference? Maybe I'm assuming too much.

Dr. FREDRICKSON. The difference is rooted in fact that you might be able to create new organisms that would be dramatically different from what you would get through either mutagenesis or by breeding techniques, and that such a new organism might take up a new niche in the environment. This type of thinking has led to great public interest in recombinant DNA technology.

There are also romantic reasons why I think we are more concerned about recombinant DNA techniques, because there is a confused and mistaken public perception that the use of these techniques will lead automatically to different kinds of so-called genetic engineering, to the cloning of one species of man. These are truly romantic distortions of the capability of such techniques at the present time, and have no relationship to the intent for which they're now being used.

I think that perhaps it is both of these things that have led to this extraordinary degree of concern about recombinant DNA techniques.

Mr. BROWN. Modern science and modern man, in the pursuit of efficiency and progress, have practically concentrated biological development on a very small number of food plants and other useful plants, on the order of a few dozen out of thousands of plants that constitute the genetic pool.

There is some indication that this may pose future hazards for mankind, that as we lose the diverse strains in the genetic pool and concentrate on these genetically superior types that we have developed, we may find ourselves running into real trouble sometime.

Now, there's no hazard involved in the kind of research that produced these—at least none that I know of—in the laboratory, yet maybe the future of man's health on Earth is threatened by it.

If the worst catastrophe were to occur and we were to lose the genetic diversity that exists in the biosphere, what does this say to your concentration on laboratory safety as the only factor to consider in dealing with DNA, recombinant DNA research?

Dr. FREDRICKSON. Well, I think you are quite correct. We've already learned from the tragic experiments of a social sort in Germany in the forties about the concentration on single genetic species, and we know from many practical examples the virtues of hybridization.

I suppose from the laboratory standpoint, it is that the ability to use recombinant DNA techniques that maximize the capacity for hybridization.

Dr. FREDRICKSON. I quite agree with that. The presumed or hypothetical hazards of the use of these kinds of techniques do not know any international boundaries, so what occurs in one part of the world could easily affect all parts of the world, and thus conformity and uniformity is extremely desirable. In fact it's necessary, if this is not to become a charade.

As I indicated before, I find—and so do many others—that there is ample evidence throughout the scientific community of agreement to a certain set of standards, the willingness to abide by guidelines, to be regulated.

I think that the steps that must now occur toward progression to an international agreement are wise and rational actions here in this country, and in those other countries that are the leaders of the scientific community that will offer effective and usable mechanisms that could be adapted to every country. There will be some differences, of course, within laws.

This is now an exercise in international law which is far more difficult to achieve than legislation within national boundaries. Nevertheless, the adoption of a sensible mode of dealing with this problem here will have a dramatically helpful effect, in my view, on the ability of other countries to persuade themselves, their scientists, their governments, and their people that here is a mode of regulation which can be used everywhere.

We are close to uniformity in the guidelines that are now extant. Only a week ago, we established through continuing conversations with molecular biologists in Britain and Europe a first meeting on the definitions of physical containment that are so explicitly spelled out in the NIH guidelines. Our aim was to begin talking: Can we develop a completely common language so that one set of descriptors will mean the same thing in every laboratory around the world that might employ recombinant DNA techniques?

We have some distance to go, as is common in seeking diplomatic solutions, in coming to agreement. But I see encouraging signs that agreement will be possible. And, while this was a trial which involved only members of the European Economic Community and the United States in very informal discussions, I'm convinced that through the WHO and through the International Council of Scientific Unions, we have the capability for involving other countries.

I think it depends very much on how well we carry off this delicate exercise here at home.

Chairman THORNTON. Thank you very much for that observation.

Mr. Brown?

Mr. BROWN. Dr. Fredrickson, as Mr. Thornton has pointed out, scientific effort to modify gene structures is not a new situation in this country. It's reflected in hybrid corn and high-yield wheat and racehorses and show dogs and a lot of other things.

Is this not correct?

Dr. FREDRICKSON. That's quite true, Mr. Brown.

Mr. BROWN. The difference between that and the recombinant situation is what? The time scale? We can now do it immediately by the proper gene manipulation?

Dr. FREDRICKSON. Yes; there is a difference in time scale, that is, one may be able to do it on command within the laboratory setting.

Finally, I want to note that biomedical research is entering a new era in its relationship to society, as represented by the debate over this legislation. Research is passing from an extended period of relative privacy and autonomy to an engagement with what must be called new ethical, legal, and social imperatives under concerned public scrutiny.

The National Institutes of Health have responded to these concerns by requiring the formation of review boards to oversee experimentation involving human subjects, animal care, and most recently for overseeing DNA recombinant experiments. Similar bodies may soon have to oversee other hazardous laboratory work.

These responsibilities are inescapable adjustments to the rising demands for public governance of science, though this need not—and, indeed, I think should not—go beyond what is clearly required for public safety, lest we inadvertently impede successful research and hamper creativity.

In the main, the progress of science will continue to depend on the initiative and insights—call it inspiration, if you like—of individual scientists.

Thank you, Mr. Chairman. I shall be delighted to answer any further questions you or the committee might have.

Chairman THORNTON. Thank you very much, Dr. Fredrickson, for your excellent presentation, and for the longer presentation which has been made a part of the record.

At the outset, I would like to ask one question which was addressed to previous witnesses, and that is: What is the rationale for drawing a distinction in regulatory policy between recombinant DNA molecule research and other forms of genetic engineering or genetic manipulation which, while they might not meet the precise scientific definition of recombinant DNA research, could, if I understand it correctly, result in many of the same hazards which are perceived by the public as being consequent upon DNA research?

I submit, for example, the General Electric experiments which involved the transfer of plasmids which had not been recombined into other bacteria, and which did have an effect upon the gene structure of the host bacteria, but was not, as I understand it, technically recombinant DNA research; yet it seems to have many of the same consequences?

Can you comment on how and why such a line should be drawn?

Dr. FREDRICKSON. Yes; that's an extremely important question, and one which has been a matter of concern to all of us who both do science and must be responsible for some of its administration.

I shall answer the question primarily in this way: As one deals with the many aspects of genetic recombination, one comes to the realization that there is almost no boundary to this problem. As you are aware, there are techniques other than recombinant DNA for changing the genetic material in species, simple breeding between members of the same species is one example. I suppose the most outrageous example is springtime itself, which is a fortunate, recurrent exercise in recombination, which is almost beyond control, and clearly is something which is an example of the recombination which has resulted in our being what we are today.

Respectfully submitted,

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Staff Scientist
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November 11, 1976

(c) Whether or not a strain of bacteria should be sought and studied to replace E. coli as the subject of most recombinant DNA experiments before this work be allowed to proceed.

(d) Whether or not an "ordinary" or normal, non-hazardous gene from one organism might become dangerous if expressed in the wrong place and wrong time in the wrong organism (this important question was virtually ignored by the advisory committee).

A legislative-type hearing conducted by HEW is the best forum for full consideration of the issues raised by recombinant DNA research and technology. In effect, such a hearing would amount to a broad-based public review of the existing NIH guidelines and would permit open debate on issues given little or no attention by the NIH Drafting Committee or the office of the director. Whether the activity is transportation of recombinant DNA materials, research, commercial production or use in the environment, HEW has the authority to regulate corporations and scientists whether or not they receive federal research support. Therefore, it is highly appropriate for HEW to hold such a hearing.

B. Final Regulations Governing All Parties Engaged

Promulgation of the NIH guidelines reflects a consensus that recombinant DNA research and technology pose a sufficient hazard to the public health and the environment to require the prohibition of some experiments and the imposition of safety

Although this meeting was not well publicized, many scientists, public interest groups and laymen were invited to attend and to comment on the guidelines.[2/] Additional input was sought from these same individuals during the two-month period following this meeting. A considerable body of material was received by commentators by the office of the Director of NIH, and is summarized, in part, in the Decision of the Director, NIH, to Release Guidelines for Research on Recombinant DNA Molecules (see 41 Fed. Reg. No. 131, pp. 27902-27911, July 7, 1976).

Little discussion was devoted to whether or not these experiments ought to be performed at all, even though the question was raised both by concerned laymen and by prominent scientists. That there is an intrinsic and even necessary good in recombinant DNA research has been a tacit assumption on the part of the NIH advisory committee which drafted the guidelines from the onset of its deliberations. We believe that this is, at least in part, a reflection of the fact that many of the committee members are now doing recombinant DNA research and have a vested interest in its future. In the public meeting held on February 9-10, 1976, the request was made that such potentially hazardous research should at least await the development of a strain of bacteria which is not a ubiquitous inhabitant of the human colon. E. coli is the current organism of choice simply because a large body of genetic information exists concerning this bacterium. This

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2/ A copy of the comments submitted by EDF at that time are attached as Appendix 1.

disease illustrate that the Secretary has the authority under §361 to regulate infectious agents from any source, transmitted by any means

Because microorganisms produced by recombinant DNA activities may spread disease among humans, it has already been recognized that regulations promulgated pursuant to authority under §361 control transportation of DNA materials. Section II-C of the NIH Guidelines (41 Fed. Reg. 27914) states that the shipment of recombinant DNA materials is governed by 42 C.F.R. §72.25 which specifies safety requirements for the transportation of etiologic agents.[1/] An "etiologic agent" is defined as ". . . a viable microorganism or its toxin which causes, or may cause, human disease." (42 C.F.R. §72.25(a)(1)) Recombinant research and the commercial use of recombinant technology pose an even greater risk that the public will be exposed to infectious agents than does transportation. The same risk of communicable disease which gives the Secretary the authority to regulate the transportation of recombinant materials under §361 gives him the authority to regulate all recombinant DNA activities.

V. Relief

By this petition EDF and NRDC seek the following relief:

1. A legislative-type hearing to develop a policy on recombinant DNA research and technology.

2. Regulations binding on all parties conducting recombinant DNA research or otherwise engaged in recombinant DNA technology.

1/ §72.25 applies to microorganisms listed in subsection (C) which includes most microorganisms used in recombinant DNA research such as E. coli, Simian Viruses, Salmonella.

While EDF and NRDC commend the monumental effort made by NIH to regulate this potentially hazardous branch of research within its own jurisdiction, we are disturbed by the fact that the guidelines cover only NIH supported research, leaving large segments of the scientific and industrial communities subject to no required safety procedures. Recombinant DNA research and technology is now being pursued and supported by private corporations, agencies of the Federal government, as well as scientists at universities and private institutions.

General Electric is trying to develop a bacteria which can degrade petroleum and could be used to consume oil spills. Imperial Chemical Industries Ltd. (ICI) of Britain is trying to develop a virus which produces insulin. (Janice Crossland, "Hands on the Code", Environment 18:6, September 1976). The drug industry in the United States has also expressed interest in the commercial use of recombinant DNA techniques. Federal agencies such as the Department of Defense may contemplate conducting experiments. Scientists at universities whether they receive government grants or not are conducting recombinant DNA research. Therefore, we consider a uniform set of regulations covering all parties engaging in recombinant DNA research to be absolutely necessary.

IV. The Secretary of HEW Has the Authority To Regulate All Recombinant DNA Activities

Section 361 of the Public Health Services Act (42 U.S.C. §264) gives the Secretary of Health, Education and Welfare the authority to regulate all recombinant DNA research and technology. The Section empowers the Secretary to:

> ". . . make and enforce such regulations as in his judgement are necessary to prevent the introduction, transmission, or spread of communicable

virus, which also produces tumors in animals, which are the primary objects of recombinant DNA research in animal viruses.

5. The virulence of influenza virus, and the spontaneous occurrence in nature at certain times of devastating flu epidemics (such as the one of 1918) is apparently controlled by the reassortment in nature of the 12 subunits of the viral RNA[1/]. Yet the genetic basis and the mechanism by which these viruses are rendered highly virulent is not understood. Again, therefore, any recombinant DNA procedure involving any animal virus or cells containing such a virus must be considered to pose the risk of creating highly virulent or infectious strains.

6. The expression of <u>any</u> foreign gene, however seemingly innocuous it may be in the cells of a human or other mammal, whether inserted by viral infection or some other mechanism, poses the risk that a protein will be produced in the infected cells which has never been seen by the host's immune system. Thus the possibility of an auto immune disease exists (as in rheumatic fever or degenerative kidney disease) in which the body produces antibodies against proteins within or produced by its own cells, ultimately destroying the cells themselves. The NIH guidelines discuss "harmful" genes in the sense of DNA specifying antibiotic resistance factors or protein toxins.

1/ Davis, et al., <u>supra</u> at 1318. RNA = rihonucleic acid. Some viruses contain RNA rather than DNA.

expand this list to include additional untoward health effects. The following are examples of potential threats to human health which could result from recombinant DNA research and technology:

1. Most of the proposed and ongoing recombinant DNA research involves strains of the bacterium Escherichia coli (E. coli) as a host for plasmids containing DNA from other sources. E. coli is a common resident of the human colon, is responsible for nearly 100% of human upper urinary tract infections[1] and for approximately 30-40% of the cases of sepsis[2] (infection of the human bloodstream), which is often fatal. While the strains of E. coli used in recombinant DNA research (variants of strain K-12) do not normally colonize the human colon, they can under unusual conditions, particularly in patients weakened by another disease state. Perhaps more serious, however, is the capacity of K-12 strains of E. coli to exchange DNA with other similar or related organisms.[3] Genetic exchange between E. coli and strains of Salmonella,[4] a human pathogen, is well documented. Since the genetic determinants in infectivity and virulence of bacteria are not understood, one must consider the possibility that even a seemingly trivial modification of the E. coli genome might greatly alter its capacity for infection and propagation within humans.

1/ B. D. Davis, et al., Microbiology 768 (2nd ed. 1973).

2/ Dr. Halsted Holman - Oral testimony before a hearing of the Subcommittee on Health of the Senate Committee on Labor and Public Welfare, Sept. 22, 1976

3/ Davis, et al., supra at 182-200.

4/ Id. at 194.

protection of the human environment. NRDC has 24,000 members and contributors in the United States. Many of these persons and their children will be subjected to the increased risk of adverse health effects discussed in pp. 9 - 12, infra, if the Secretary does not adopt effective regulations controlling the relevant procedures. Among the methods NRDC uses to achieve its objectives are: (1) improving federal agency decision-making which affects the environment by commenting, furnishing information, participating in administrative proceedings, and bringing lawsuits where legal duties are not being fulfilled; and (2) improving federal agency decision-making which affects the environment by encouraging agencies to solicit and utilize the views, knowledge, and expertise of members of the general public.

III. The Need to Control Recombinant DNA Research and Technology in the Interest of Public Health

The techniques defined above enable scientists to recombine the DNA from two unrelated species and, thus, construct organisms which may express genes from biologically unrelated sources. Because the properties of such deliberately or accidentally constructed organisms are unknown and may represent hitherto nonexistent hazards both to human health and the ecology, members of the scientific community have raised the questions of whether or not proceeding with this type of research at this time is prudent, and, if so, whether or not the public and the environment can be adequately protected

DNA molecules or the products derived therefrom. NRDC and EDF seek regulations governing all recombinant DNA research and technology including, but not limited to:

(a) All experiments discussed in the "Guidelines for Research Involving Recombinant DNA Molecules" issued by the National Institutes of Health on June 23, 1976 and published in the Federal Register Part II on July 7, 1976;

(b) All experiments in which chemically or enzymatically synthesized DNA is inserted into a living host, plasmid or virus; and

(c) All other procedures in which DNA from any two sources which do not normally exchange genetic information may function within the same cell.

NRDC and EDF seek regulations which would cover all persons and organizations conducting or supporting recombinant DNA research including, but not limited to:

1. Recipients of Research grants awarded by any agency within the Department of Health, Education and Welfare;
2. Private corporations;
3. Private and public universities; and
4. Other departments and agencies of the Federal Government.

recombinant DNA research and technology but rather the beginning of full public consideration of all relevant issues.

The guidelines apply only to recombinant DNA research supported by the NIH. While Dr. Donald Fredrickson, the director of NIH, has called on all government agencies and "all who support or conduct such research throughout the United States" (41 Fed. Reg. No. 131, p. 27906, July 7, 1976) to voluntarily adopt the NIH guidelines, only the National Science Foundation, Department of Defense, and the Energy Research and Development Administration have formally done so.* Therefore, a significant portion of recombinant DNA research and technology is not covered by any mandatory set of safety procedures, leaving the public unprotected from its potential hazards. Furthermore, it is the position of the petitioners that the public did not have an adequate opportunity to participate in the basic policy decisions underlying the NIH Guidelines.

For these reasons, EDF and NRDC request that: (1) a public hearing of broader scope than those held this year at NIH be held on the questions of to what extent and under what conditions recombinant DNA research and technology should be allowed to proceed; (2) final regulations be promulgated based on the record of that hearing which would apply to all recombinant DNA research and technology in the

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* Dr. Joe Perpich, National Institutes of Health, personal communication.

UNITED STATES OF AMERICA

BEFORE THE

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

PETITION OF ENVIRONMENTAL DEFENSE FUND, INC.
AND NATURAL RESOURCES DEFENSE COUNCIL, INC.
TO THE SECRETARY OF HEALTH, EDUCATION AND WELFARE
TO HOLD HEARINGS AND PROMULGATE REGULATIONS UNDER
THE PUBLIC HEALTH SERVICE ACT GOVERNING RECOMBINANT
DNA ACTIVITIES

The Environmental Defense Fund (EDF) and the Natural Resources Defense Council (NRDC) hereby petition the Secretary of Health, Education and Welfare (hereafter "the Secretary") under the authority granted him by §361 of the Public Health Services Act (42 U.S.C. §264) to hold public hearings and promulgate regulations governing recombinant DNA[1/] research and technology in which fragments of DNA from different organisms, cells or viruses are combined in novel ways and introduced into a living host organism or cell.

1/ DNA - deoxyribonucleic acid, the chemical substance which contains all genetic information.

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Dr. Burke Zimmerman
Staff Scientist
Environmental Defense Fund
1525 18th Street N.W.
Washington, D. C. 20036

Dear Dr. Zimmerman:

The controversy over recombinant DNA research has brought one of the most important facets of biomedical research out into the open. Although there are substantial benefits that may accrue from the research, there is also the possibility of enormous costs, both short and long term.

The public is being asked to support this research, both with its tax dollars and by being in the physical vicinity of the recombinant DNA research laboratories. Fortunately, some public inquiry has begun in the form of open hearings on the subject. These public hearings have been held in Cambridge, New York City and San Diego, and have expressed deep concern over how and whether this research should be continued.

The public at large, however, is still in the dark concerning the relevant issues in the debate. The scientific jargon that accompanies the discussion within the scientific community is, at best, confusing to non-scientists. There is an overwhelming need for accurate, up-to-date information, with the issues clearly presented in terms understandable to all of us. The public, government officials, and members of the Legislature are in need of this information. Only with substantantive understanding of all the issues will effective programs and regulations be promulgated.

CALIFORNIA INSTITUTE OF TECHNOLOGY

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DIVISION OF BIOLOGY 156-29

October 28, 1976

Dr. A. Karim Ahmed
Natural Resources Defense Council, Inc.
15 West 44th Street
New York, New York 10036

Dear Dr. Ahmed:

I am pleased to support the petition of the Environmental Defense Fund and the National Resources Defense Council to the Secretary of Health, Education and Welfare concerning recombinant DNA activities. This petition has two components: the first requests the Secretary to promulgate interim regulations to make the present NIH Guidelines concerning recombinant DNA research binding on all parties engaged in recombinant DNA research in the United States. The second requests the Secretary to conduct a "legislative-type" hearing to obtain very broadly based testimony which might guide a reformulation of the present recombinant DNA Guidelines, taking into consideration issues not addressed and points of view not presented during their development.

The Guidelines have been developed out of the concept that there is a potential hazard to public health in certain forms of recombinant DNA research. It is evident that this hazard is not restricted to recombinant DNA research conducted with the aid of NIH (or other Federal) funds. I therefore support their extension to cover all research activity in this field, however supported and wherever performed. This research does not require elaborate facilities and large capital investment. There is, therefore, no reason to believe that it will be limited to large institutions or industrial concerns with proven records of responsibility. Further, the virtual certainty of the development of new techniques and of the extension of these techniques to additional organisms and higher life forms will require a free flow of information, a continuing updating of guidelines, and the continuing scrutiny of this field of research by a body which will endeavor to reflect the public interest.

The need to consider the reformulation of the Guidelines derives from the perception that they were developed from too narrow a perspective. In my opinion the Guidelines were developed to address solely the immediate medical

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In Washington Research Project, Inc., v. Department of Health, Education, and Welfare, et al., the same court had ruled in 1974 that research designs submitted in certain NIMH grant applications are not "trade secrets" within the meaning of exemption 4. However, in that case the court noted". . .the burden of showing the trade or commercial character of the research design information was on the agency, and. . .it did not introduce a single fact relating to the commercial character of any specific research project. . . ." Thus, Washington Research Project would not appear to govern situations in which the agency could show that patentable information or similar proprietary matter was involved.

3. While it would be desirable from a scientific standpoint to retain the flexibility to modify at least some parts of the Guidelines without the delays attendant to the rulemaking process, most regulatory legislation must be implemented by regulations promulgated in accordance with the Administrative Procedures Act (APA) or similar rulemaking procedures. One approach which might overcome this problem would be to publish regulations which set forth general standards but rely on cross references to the Guidelines with respect to specific details. However, this could present enforcement problems because any enforcement action based on a cross reference could be challenged for noncompliance with the APA. For this reason, a regulatory agency would probably insist upon specificity in its regulations.

enforce. . .such regulations as in his [the Secretary's] judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases. . .from one State. . .into any other State. . . ."

Both DOT and CDC, in implementing the HMTA and section 361 with respect to biological products, have essentially aimed just at imposing labeling, packaging, and shipping requirements. This approach is in line with the statutory language which emphasizes movement. Section 361 could perhaps be interpreted more broadly to serve as legal support for more comprehensive regulation. However, in order to do so there would presumably have to be a reasonable basis for concluding that the products of all recombinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced.

Under section 353 of the PHS Act, however, CDC does have general authority to license and control the operation of clinical laboratories. While this authority would not in general have applicability to research laborarories, CDC's experience in implementing this legislation, which imposes comprehensive requirements on clinical laboratories, could be of value in the implementation of any new legislation needed to regulate laboratories conducting recombinant DNA research.

OTHER ISSUES CONSIDERED

1. In the event new legislation is sought, a model for the