Part III
Institutions and Society

Chapter 10

The Question of Risk

Chapter 10

Figures

Chapter 10

The Question of Risk

Introduction

The perception that the genetic manipulation of micro-organisms might give rise to unforeseen risks is not new. The originators of chemical mutagenesis in the 1940's were warned that harmful uncontrolled mutations might be induced by their techniques. In a letter to the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) in December of 1979, a pioneer in genetic transformation at the Rockefeller University, wrote: ". . . I did in 1950, after some deliberation, perform the first drug resistance DNA transformations, and in 1964 and 1965 took part in early warnings against indiscriminate 'transformations' that were then being imagined."[1]

[1] Ehkiss *Recombinant* ***Recombinant DNA Research, vol. 5,*** **publication No. 80-2130, March 1980, 484.**

Yet **none of this earlier public concern led to as great a controversy as has research with recombinant DNA (rDNA). No doubt it was encouraged because scientists themselves raised questions of potential hazard. The subsequent open debates among the scientists strengthened the public's perception that there was legitimate cause for concern, This has led to a continuing attempt to define the potential hazards and the chances that they might** occur.

The initial fear of harm

For the purposes of this discussion, harm (or injury) is defined as any undesirable consequence of an act. Such a broad definition is warranted by the broad targets for hypothetical harm that genetic manipulation presents: injury to an individual's health, to animals, to the environment.

The inital concern involved injury to human health. Specifically, it was feared that combining the DNA of simian virus 40, or SV40, with an *Escherichia coli* plasmid would establish a new route for the dissemination of the virus. **Although the SV40 is harmless to the monkeys from which it is obtained, it can cause cancer when injected into mice and hamsters. And while it has not been shown to cause cancer in humans, it does cause human cells to behave like cancer cells when they are grown in tissue culture. What effect such viruses might have if they were inserted** into ***E. coli,*** a normal inhabitant of the human intestine, was unknown. This uncertainty, combined with an intuitive judgment, led to a concern that something might go wrong. The dangerous scenario went as follows:

- SV40 causes cells in tissue culture to behave like cancer cells,
- SV40-carrying ***E. coli*** might be injected accidently into humans,
- humans would be exposed to SV40 in their intestines, and
- an epidemic of cancer would result.

This chain of connections, while loose, was strong enough to raise questions in at least some people's minds.

The virus SV40 has never actually been shown to cause cancer in humans; but the potential hazards led the Committee on Recombinant DNA Molecules of the National Academy of Sciences (NAS) to call in 1974 for a deferment of any experiments that attempted to join the DNA of a cancer-causing or other animal virus to vector DNA. At the same time, other experiments,

76-565 0 - 81 - 14

that were thought to have a potential for harm –particularly those that were designed to transfer genes for potent toxins or for resistance to antibiotics into bacteria of a different species—were also deferred. Finally, one other type of experiment, in which genes from higher organisms might have been combined with vectors, was to be postponed. The fear was that latent "cancer-causing genes" might be inadvertently passed on to E. coli.

Throughout the moratorium, one point was certain: no evidence existed to show that harm would come from these experiments. But it was a possibility, The scientists who originally raised questions wrote in 1975: ". . . few, if any, believe that this methodology is free from risk. "[2] It was recognized at that time that ". . . estimating the risks will be difficult and intuitive at first but this will improve as we acquire additional knowledge. "[3] Hence two principles were to be followed: containment of the micro-organisms (see table 35, p. 213) was to be an essential part of any experiment; and the level of containment was to match the estimated risk. These principles were incorporated into the Guidelines for Research Involving Recombinant DNA Molecules, promulgated by NIH in 1976.

But the original fears surrounding rDNA research progressed beyond concern that humans might be harmed. Ecological harm to plants, animals, and the inanimate world were also considered. And other critics noted the possibility of moral and ethical harm, which might disrupt both society's structure and its system of values.

Classification of potential "physical harm

Some combinations of DNA may be harmful to man or his environment—e.g., if an entire DNA copy of the poliovirus genetic material is combined with E. coli plasmid DNA, few would argue against the need for careful handling of this material.

For practical purposes, the potential harm associated with various micro-organisms is shown in figure 35. Each letter (A through L) represents the consequence of a particular combination of events and micro-organisms. For example, the letters:

- A, C represent the ***intentional release of micro-organisms known to be harmful*** to the environment or to man—e.g., in biological warfare or terrorism.
- B, D represent the ***inadvertent release of micro-organisms known to be harmful*** to the **environment or to man—e.g., in accidents at high-containment facilities where work is being carried out with dangerous micro-organisms.**
- E, I **represent the *intentional release of micro-organisms thought to be safe*** but which ***prove harmful—when* the safety of organisms has been misjudged.**
- F, J **represent the *intentional release*** of ***micro-organisms which prove safe*** as expected—e.g., in oil recovery, mining, agriculture, and pollution control.
- H, L represent the ***inadvertent release of micro-organisms which have no harmful consequences— e.g.,*** in ordinary accidents with harmless micro-organisms.
- G, K represent the ***inadvertent release of micro-organisms thought to be*** **safe** but which ***prove harmful—the*** most unlikely possible consequence, because both an accident must occur and a misjudgment about the safety must have been made.

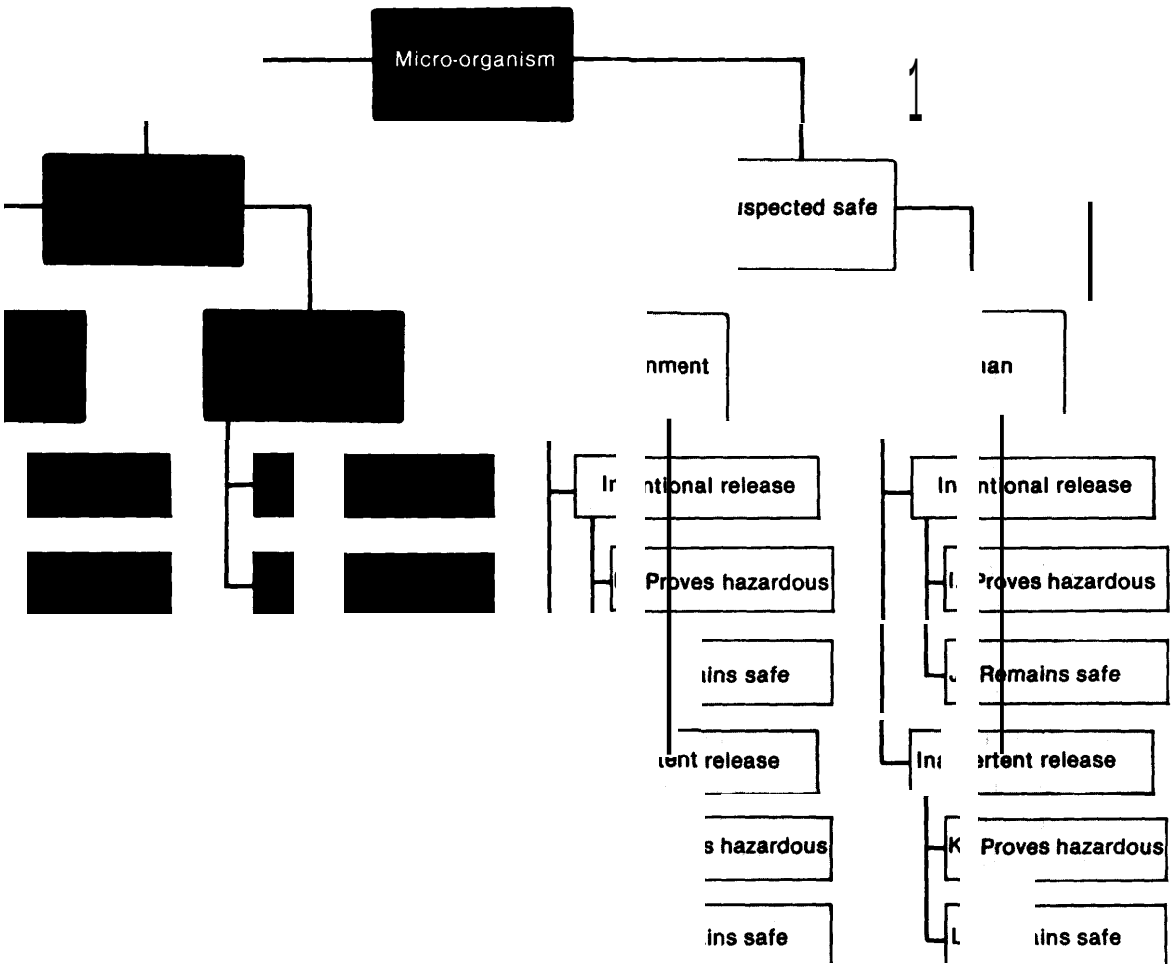
Discussions of physical harm have recognized the possibility of intentional misuse but have minimized its likelihood. The Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction which was ratified by both the Senate and the President in 1975, * states that the signatories will "never develop . . . biological agents or toxins . . . that have no justification for prophylactic, protective, or other peaceful purposes. " Such a provision clearly includes micro-organisms carrying rDNA molecules or the toxins

[2] *DNA Research, vol.* **1, DHEW publication No.** blicat **76-1138,** 76- **1976,** u **59.**

the Prohibition p the Development, Production, and Stockpiling of ockpiling of Bacteriologica **and** ologica **Weapons and on Their Destruction,** Destruction, Washingt **and Moscow, Apr. 10, 1972; entered into force on Mar.** re **1975 (26 [J.** 19 **583).**

***As of 1980,** As **countries** o **ratified the treaty; another** ty **have but not ratified.**

Figure 35.—Flow Chart of Possible Consequences of Using Genetically Engineered Micro-Organisms



SOURCE: Office of Technology Assessment.

produced by them. It must be assumed that those who signed did so in good faith.

While there is no way to judge the likelihood of developments in this area, the problems that would accompany any attempt to use pathogenic micro-organisms in warfare—difficulties in controlling spread, protection of one's own troops and population—tend to discourage the use of genetic engineering for this purpose. * Similarly, the danger that these techniques might be used by terrorists is lessened by the **scientific sophistication needed to construct a more virulent organism than those that can** already be obtained—e.g., encephalitis viruses or toxin-producing bacteria like C. ***botulinum*** or C. ***tetani.***

Some discussions have centered around the possibility of accidents caused by a break in containment. Construction of potentially harmful micro-organisms will probably continue to be prohibited by the Guidelines; exceptions will be made only under the most extraordinary circumstances. To date, no organism known to be more harmful than the organism serving as the source of DNA has been constructed.

However, the biggest controversy has centered around unforeseen harm—that micro-organisms thought safe might prove harmful.

* **is prohibited,** into is

Discussion of this kind of harm is hindered by the difficulty not only of quantifying the probability of an occurrence but also of predicting the type of damage that might occur. The different types of damage that can be conjured up are limited only by imagination. The scenarios have included epidemics of cancer, the spread of oil-eating bacteria, the uncontrolled proliferation of new plant life; and infection with hormone-producing bacteria.

The ***risk*** of harm refers to the chance of harm actually occurring. In the present controversy, it has been difficult to distinguish the possible from the probable. It is, for instance, possible that an individual will be killed by a meteor falling to the ground, but it is not probable. Analogous situations exist in genetic engineering. It is in this analysis that debate over genetic engineering has some special elements: the uncertainty of what kind of harm could occur, the uncertainty about the magnitude of risk, and the problem of the perception of risk.

Identification of possible harm

The first step in estimating risk is identifying the potential harm. It is not very meaningful to ask: How much risk does rDNA pose? The concept of risk takes on meaning only when harm is identified. The question should be: What is the likelihood that rDNA will cause a specific disease such as in a single individual or in an entire population? The magnitude of the possible harm is incorporated in the question of risk, but differs in the two cases. A statement about the risk of death to one person is different than one about the risk of death to a thousand. The right questions must be asked about a specific harm.

Since no dangerous accidents are known to have occurred, their types remain conjectural. Identifying potential harm rests on intuition and arguments based on analogy. Even a so-called risk experiment is an approximation of subsequent genetic manipulations. That is why experts disagree. No incontestable "scientific method" dictates which analogy is useful or acceptable. By their very nature, all analogies share some characteristics with the event under consideration but differ in others. The goal is to discover the one that is most similar and to observe it often. This process then forms the basis for extrapolation.

For example, it has been argued that ecological damage can be caused by the introduction of plants, animals, and micro-organisms into new environments. Scores of examples from history support this conclusion. The introduction to the United States of the Brazilian water hyacinth in the late 19th century has led to an infestation of the Southern waterways. Uncontrolled spread of English sparrows originally imported to control insects has made eradication programs necessary. Countless other examples are confirmation that biological organisms may, at times, cause ecological damage when introduced into a new environment. Yet there is no agreement on whether such analogies are particularly relevant to assessing potential dangers from genetically engineered organisms. It could be argued-e.g., that a genetically engineered organism (carrying less than 1 percent new genes) is still over 99 percent the same as the original, and is therefore not analogous to the "totally new" organism introduced into an ecosystem. Some experts emphasize the differences between the situations; others emphasize the similarities.

Other analogies have been raised. New strains of influenza virus arise regularly. Some can cause epidemics because the population, never before exposed to them, carries no protective antibodies. Yet can this analogy suggest that relatively harmless strains of E. ***coli*** might be transformed into epidemic pathogens? There is disagreement, and debates continue about what "could happen" or what is even logically possible.

Estimates of harm: risk

Assuming that agreement has been reached on the ***possibility*** of a specific harm, what can be done to ascertain the ***probability?*** What is the likelihood that damage will occur?

Damage invariably occurs as the result of a ***series*** of events, each of which has its own particular chance of occurring. Flow charts have been prepared to identify these steps. A typical

analysis determines a probability value for each step-e. g., in figure 36 step II the probability of escape can be estimated based on the historical record of experiments with micro- organisms. Depending on the degree of containment, the probability varies. It is almost certain that experiments on an open bench top, using no precautions, will result in some escape to the surrounding environment—a much less likely event in maximum containment facilities. (See table 35.)

Two points should be noted. First, each probability can be minimized by appropriate control measures. Second, the probability that the final event will occur is equal to or less likely than the least likely link in the chain. Because the probabilities must be multiplied together, if the probability of any single step is zero, the probability of the final outcome is zero; the chain of events is broken.

THE STATUS OF THE CURRENT ASSESSMENT OF PHYSICAL RISK

A **successful risk assessment should provide information about the likelihood and magnitude of damage that might occur under given** circumstances. It is clear that the more types of damage that are identified, the more risk assessments must be carried out.

Figure 36.— Flow Chart to Establish Probability of Harm Caused by the Escape of a Micro-Organism Carrying Recombinant DNA

Event	Probability
L Inadvertent incorporation of hazardous gene into micro-organism	P_1
11. Escape of micro-organism into environment	P_2
III. Multiplication of micro-organism and establishment in ecological niche	P_3
ı of man	P*
V. Production of factor to cause disease	

NOTE: P_5 will always be smaller than any of the other probabilities.

SOURCE: Office of Technology Assessment.

Although the original charter of RAC underscored the importance of a risk assessment program, it was not until 1979 that the details of a formal program were published. For 5 years, risks were assessed on a case-by-case basis through: 1) experiments carried out under contract from NIH, 2) experiments that were designed for other purposes but which proved to be relevant to the question of risk, and 3) conferences at which findings were examined.

From the start, it was difficult to design experiments that could supply meaningful information-e.g., how does one test the possibility that "massive ecological disruptions might occur?" Or that a new bacterium with harmful unforseen characteristics will emerge? Still some experiments were proposed. But because these experiments had to be approximations of the actual situation, the applicability of their findings was debated. Here too, experts could and did disagree—not about the findings themselves, but about their interpretation.

For example, in an important experiment designed to test a "worst case situation, " a tumor virus called polyoma was found to cause ***no*** tumors in test animals when incorporated into E. coli.[5]* Since just a few molecules of the viral DNA are known to cause tumors when injected directly into animals, it was concluded that tumor viruses are noninfectious to animals when incorporated into E. ***coli.*** If polyoma virus, which is the most infective tumor virus known for hamsters, cannot cause tumors in the rDNA state in E. ***coli,*** it is unlikely that other tumor viruses will do so. This conclusion has had widespread, but not unanimous, acceptance. It has been argued that there might be "something special" about polyoma that prevents it from causing tumors in this altered state; other tumor viruses might still be able to do so. At one meeting of RAC, in fact, it was suggested that experiments with several other viruses be carried out to confirm the generality of the finding. But how many more viruses? What **is** enough?

---

[5] H A. Israel, H. W. Chan, W. P. Rowe, and M. A. Martin, "Molecular Cloning of Polyoma Virus DNA in *Escherichia Coli*: Plasmid Vector Systems," *Science*, 1979. *1979.*

*Some combinations of free polyoma tumor and tumor virus DNA did cause infections.

For some, one carefully planned experiment using the most sensitive tests is sufficient to allay fears. But for others, significant doubt about safety remains, regardless of how many viruses are examined. The criteria depend on an individual's ***perception*** of risk.

Many experiments carried out for purposes other than risk assessment have provided evidence that scenarios of doom or catastrophe are highly unlikely. This is the general consensus of specialists, not only in molecular biology, but in population genetics, microbiology, infectious diseases, epidemiology, and public health.

Experiments have revealed that the structure of genes from higher organisms (plants and animals) differ from those of bacteria. Consequently, those genes are unlikely to be expressed ***accidentally*** by a bacterium; the original fears of "shotgun" experiments have become less well-founded. Hence, data gathered to date have made the accidental construction of a new epidemic strain more unlikely.

Conference discussions have also contributed to a better understanding of the risks. At one such conference,[6] which was attended by 45 experts in infectious diseases and microbiology, it was concluded that:

- E. ***coli*** K-12 (the weakened form of E. coli, used in experiments) does not flourish in the intestinal tract of man;
- the type of plasmid permitted by the Guidelines has not been shown to spread from E. coli K-12 to other ***E. coli*** in the gut; and
- ***E. coli*** K-12 cannot be converted to a harmful strain even after known virulence factors were transferred to it using standard genetic techniques.

A workshop sponsored by NIH[7] provided a forum for scientists to discuss the risks posed by viruses in rDNA experiments. They concluded that the risks were probably fess when a virus was placed inside a bacterium in rDNA form than when it existed freely. * Experts in infectious disease have stressed repeatedly that the ability of a micro-organism to cause disease depends on a host of factors, all working together. Inserting a piece of DNA into a bacterium is unlikely to suddenly transform the organism into a virulent epidemic strain.

Careful calculations can also allay fears about the damage a genetically engineered micro-organism might cause. Doomsday scenarios of escaped ***E. coli*** that carry insulin or other hormone-producing genes were recently examined in another workshop.[8] Prior to this workshop, newspaper accounts raised the possibility that an ***E. coli*** carrying the gene for human insulin production might colonize humans and thus upset the hormonal balance of the body.

The participants calculated how much insulin could be produced. First, it was assumed that a series of highly unlikely events would occur—accidental release, ingestion by humans, stable colonization of the intestine by ***E. coli*** K-12. ***E. coli*** constitutes approximately 1 percent of the intestinal bacterial population, and it was assumed that all the normal ***E. coli*** would be replaced by the insulin-producing ***E. coli.*** Insulin is made in the form of a precursor molecule, proinsulin. It was assumed that 30 percent of all bacterial protein production would be devoted to this single protein, another highly unlikely situation. If so, 30 micrograms (ug)-or 0.6 units—would then be made in the intestine. Although proteins are very poorly absorbed from the intestinal cavity, it was assumed for the sake of argument that 100 percent of the proinsulin would be absorbed into the circulation. Thus, 0.6 units of insulin would be added to the normal daily human production of 25 to 30 units—an imperceptible difference.

Calculations like these have been carried out for several other hormones. Even with the most implausible series of events, leading to the greatest opportunity for hormone production,

[6] W Studies on Assessment ssessment Risks ential R With Recombinant DNA nant DNA Ex ion," entation." Falmo June , 1977.

[7] W Assess Risks ases Risks for Recomb Experiments Inv ving Viral Genomes," cosponsored by th Institutes of H the and the European H. Molecul r Biology Or , Asco t. Er 26-2&J, Jan. 2

"(hi the "Or the it Food has how this provided ass with new with viruses iruses an rea ents su os

[8] "National Allergy of infectious Diseases 011 on Re DNA Risk DNA Risk ," ssessment " Recombina 11-12, 1980.

the conclusion is that normal hormone levels would change by less than 10 percent. Similar conditions for interferon production could release approximately 70ug or the maximum daily dose currently used in cancer therapy. Long-term effects of such exposure are currently unknown; therefore, experiments using high-producing strains **(10^6** molecules per cell or more) are likely to be **monitored if such strains ever become available.**

The NIH program of risk assessment, which was formally started in 1979, continues to identify possible consequences of rDNA research. Under the aegis of the National Institute of Allergy and Infectious Diseases, the program supports research studies designed to elucidate the likelihood of harm. * In addition, it collates general data from other experiments that might be relevant to risk assessment. Other risk assessments are being conducted by European organizations * * and by the U.S. Environmental Protection Agency to assess the consequences of releasing micro-organisms into the environment.

Thus far, there is no compelling evidence that E. coli K-12 bacteria carrying rDNA will be more hazardous than any of the micro-organisms which served as the source of DNA. Nevertheless, all the experiments have dealt with one genus of bacterium. Unless the conclusions about E. *coli* can be extended to other organisms likely to be used in experiments (such as Bacillus *subtilis* and yeast), other assessments maybe appropriate.

*"Extramural efforts were first conceived in the summer of 1975 to develop and test safer host-vector systems based on *E. coli,* the interagency agreement entered into with the Naval Biosciences Laboratory tested *E. coli* systems in a series of simulated accidental spills in the laboratory. At the University of Michigan the survival of these systems was tested in mice and in cultural conditions simulating the mouse gastrointestinal tract. Tufts University tested these systems in both mice and human volunteers. Finally, the survival of host-vector systems in sewage treatment plants was tested at the University of Texas. The peak year for costs of supporting research contracts was 1978; over a half-million dollars were required. currently, the cost of maintaining the high containment facility at Frederick, Md., is between $200,000 and $250,000 annually.

**First Report to the Committee on Genetic Experimentation , a scientific committee of the International Council of Scientific Unions, from the Working Group on Risk Assessment, July 1978.

Perception of risk

The probability of damage can be estimated for various events. The entire insurance industry is based on the fact that unfavorable events occur on a regular basis. The number of people dying annually from cancer, or automobile accidents, or homicides can be predicted fairly accurately. These estimates depend on the availability of data and the assumptions that the major determinants do not change from year to year.

But even if the probability of damage is fairly well known, a gap often exists between this "real" probability of occurrence and the "perceived" probability. Two factors that tend to affect perceptions are the magnitude of the possible damage and the lack of individual control over exposure to the risk. Both of these are significant factors in the fears associated with rDNA and the manipulation of genes. Because intuitive evaluations can contradict analytical evaluations, the question of risk cannot be resolved strictly on an analytical basis. Its resolution will have to come through the political process.

BURDEN OF PROOF

The possibility of inadvertently creating a dangerous organism does exist, but its probability is lower than was originally thought. Nevertheless, an important principle emerges from the debate. Society must decide whether the burden of proof rests with those who demand evidence of safety or with those who demand evidence of hazard. The former would halt experiments until they are proved safe. The latter would continue experiments until it is shown that they might cause harm.

A significant theoretical difference exists between the two approaches. Evidence can almost always be provided to show that something causes harm—e.g., it can be demonstrated that a poliovirus causes paralysis, that a *Pneumococcus* causes pneumonia, that a rhinovirus causes the common cold. However, it cannot be demonstrated that a poliovirus can ***never*** cause the common cold, It cannot be demonstrated that rDNA molecules will ***never*** be harmful. It can

only be demonstrated that harmful events are unlikely. Hence, society must determine what level of uncertainty it is willing to accept.

Other concerns

Concerns raised by industrial applications

Originally concerns involved hazards that might arise in the laboratory. Now that there are industrial applications of genetic engineering, the concerns include:

. risks associated with the laboratory construction of new strains of organisms,
. risks associated with industrial production or consumer use of the new strains, and
risks associated with the products obtained from the new strains.

Many similar considerations apply to the assessment of the first two kinds of risks. Unless the organisms used in an industrial production scheme are thoroughly characterized, conjectured fears about their ability to cause disease will continue. Even with a recombinant organism that has a well-defined sequence of DNA, a break in containment would leave its behavior in the environment questionable. Experience with substances such as asbestos gives rise to fears that exposure to the new biological systems might also cause unforseen pathological conditions at some future time.

Hazards associated with products raise different questions. The growing consensus in Federal regulatory agencies appears to be that these products should be assessed like all others—e,g., human growth hormone (hGH) produced by genetically engineered bacteria should be tested for purity, chemical identity, and biological activity just like hGH from human pituitary glands. The possibility of product variation due to mutation of the bacteria, however, suggests that batch testing and certification might be warranted as well. (For further discussion see ch. 11.)

Concerns raised by the implications of the rDNA controversy for general microbiology

Questions about the potential harm from genetically engineered micro-organisms have led to questions about the efforts currently employed to protect the public from work being done with micro-organisms known to be hazardous. These viruses, bacteria, and fungi are handled daily in laboratory experiments, in the routine isolation of infectious agents from patients, and in the production of vaccines in the pharmaceutical industry.

Questions have been raised about the efficacy of regulations established for these various potentially hazardous agents. A full-scale assessment is not within the scope of this study, but it is clear that the questions are pertinent. Two conclusions have been reached.

First, there is a growing belief that the mere existence of a classification scheme for hazardous agents by the Center for Disease Control (CDC) is not enough to ensure their safe handling. The Subcommittee on Arbovirus Laboratory Safety was formed recently because of concerns expressed in academic circles. Representatives from universities, the Public Health Service, the U. S. Department of Agriculture, and the military, who constituted the subcommittee, are preparing a report based on an international survey of laboratory practices and infections. They found wide variation in the ways different agents were handled. Most of their recommendations are identical with those applicable to rDNA–that appropriate containment levels be used with different viruses, that the health of workers be monitored, and that an Institutional Biosafety Committee be appointed to serve each institution.

Second, little is known about the health record of workers involved in the fermentation and vaccine industries. For most industrial operations the evidence of harm is almost entirely anecdotal. Most industrial fermentations are regarded as harmless; representatives of industry characterize it as a "non-problem" that has never merited monitoring. Comprehensive information on the potential harmful effects associated with research using rDNA-carrying micro-organisms will not be available because the Guidelines consider it the responsibility of each institution or company to "determine, in connection with each project, the necessity for medical surveillance of recombinant-DNA research personnel." Hence some institutions might decide to keep records of some or all activities; others might not.

To be sure, some companies have exceeded the minimal medical standards set by NIH for fermentation using rDNA-carrying micro-organisms–e.g., Eli Lilly & Co. requires that all illnesses be reported to supervisors and that any employees who are ill for more than 5 days must report to a physician before being allowed to return to work. Any employee taking antibiotics (which might make it easier for bacteria to colonize) is restricted from areas where rDNA research is being done until 5 days after the discontinuance of the antibiotic. At Abbott Laboratories, a physician checks into the illness of any recombinant worker who is off more than 1 day–a precaution taken only after 5 days off for workers in other areas. Lilly maintains a computer listing of all workers involved in rDNA activities. Lilly, the Upjohn Co., and Merck, Sharp and Dohme have been in the process of computerizing the health records of all their employees over the past several years.

Work with rDNA has focused attention on biohazards and medical surveillance—an awareness that had arisen in the past but had not been sustained. * Consequently, several documents on the subject either have been or will be published:

- CDC is preparing a complete revision of its laboratory safety manual, which is widely used as a starting point by other laboratories.
- ***The Classification of Etiologic Agents on the Basis*** of ***Hazard,*** which was last revised in 1974, has been expanded by CDC in collaboration with NIH into a Proposed ***Biosafety Guidelines for Microbiological and Biomedical Laboratories.*** These guidelines serve the purpose fulfilled by the Dangerous Pathogens Advisory Group (DPAG) in the United Kingdom, although they lack any regulatory strength.
- A comprehensive program in safety, health, and environmental protection was developed in 1979 by and for NIH. It is administered by the Division of Safety, which includes programs in radiation safety, occupational safety and health, environmental protection, and occupational medicine.
- The Office of Biohazard Safety, National **Cancer Institute has just completed a 3-year study of the medical surveillance programs of its contractors; a report is being drafted.**

Although the academic, governmental, and industrial communities have shown growing interest in biosafety, * no Federal agency regulates the ***possession*** or ***use*** of **micro-organisms except for those highly pathogenic to animals and for interstate transport. * * Whether such regulations are necessary is an issue that extends beyond the scope of this study. Nevertheless, other countries—for instance the United Kingdom, with its DPAG—have acted on the issue. This organization functions specifically to guard against hazardous micro-organisms, by monitoring and licensing university and industrial laboratories and meting out penalties when necessary.**

• As ... September 1980, the National Institutes of occupational Health and Health and the ... Protection ... were planning to fund assessments ... the ... of current medical surveillance technology,

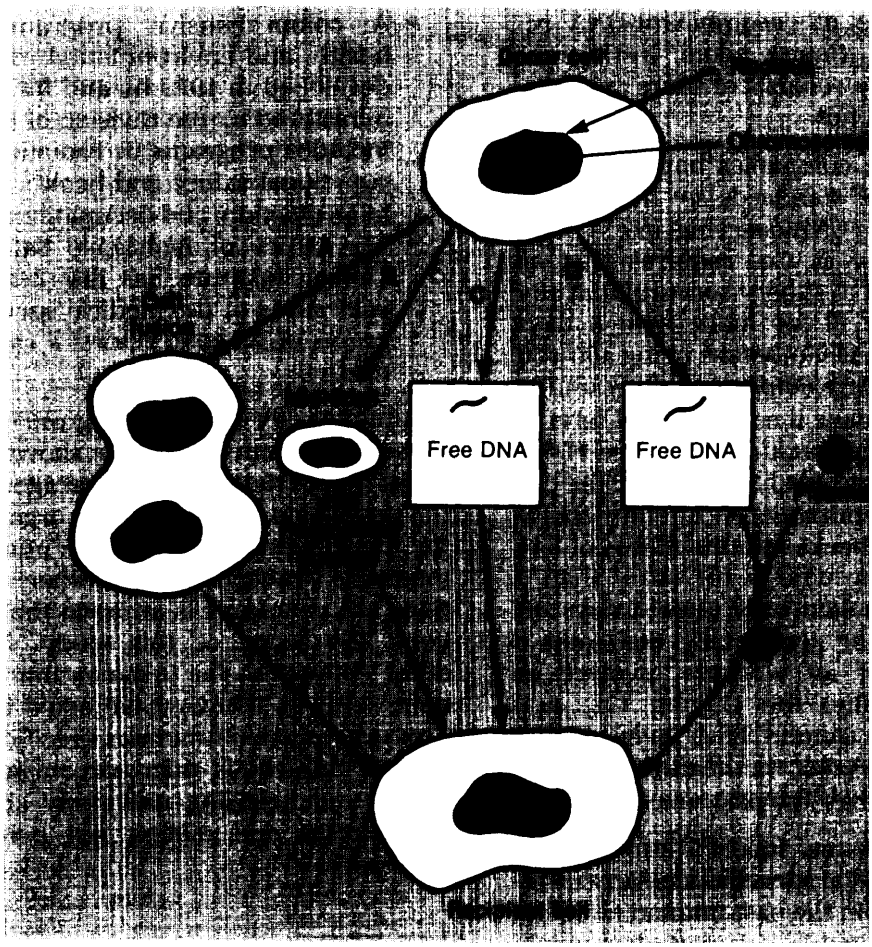
"Curiously, there is no formal society or journal, hut there has been an annual Biological ... Conference since ... conducted on a ... basis primarily by close associates ... associates of the ... Arnold G. Wedum, M. ... Director of ... Director of Industrial Health ... the U.S. ... at the ... S. Army ... Research ... Research Laboratories, Fort ... who ... Md., who is regarded as the "Father of Microbiological Safety."

• "In some States and cities, licensing is required for all facilities handling pathogenic micro-organisms.

Concerns raised by the implications of the rDNA controversy for other genetic manipulation

Altering the hereditary characteristics of an organism-by using rDNA is just one of the several methods of genetic engineering. The definition of rDNA **refers specifically to the** combination of the DNA from two organisms ***outside*** the cell. If the DNA is combined ***within*** living cells, the Guidelines do not pertain. Figure ***35*** shows several methods that achieve the same goal–transfering genetic material from one cell to another, bypassing the normal sexual mechanisms of mating. It is particularly significant that DNA from ***different species*** can be **combined by all these mechanisms, only one of** which is rDNA. Different species of bacteria,

Figure 37.-Alternative Methods for Transferring DNA From One Cell to Another



A. The two cells are fused in toto
B. A R A with a fragmented nucleus carries the DNA
C. Free DNA can enter the recipient cell in a number of ways: by waves, by direct micro through calcium-mediated transformation, or by being coated with a d with a pho membrane in order to fuse with the recipient cell
D. The free DNA can be joined to a joined to and transferred as recombinant DNA

SOURCE: Office of Technology Assessment.

fungi, and higher organisms can all be fused or manipulated. *

Opponents of rDNA have stated that combining genes from different species may disturb an extremely intricate ecological interaction that is only dimly understood. Hence, such experiments, it is argued, are unpredictable and therefore hazardous. If so, all the other methods represented in figure 35 should be included in the Guidelines. Yet they are not.

The most acceptable explanation for this inconsistency is that rDNA is currently the most efficient and successful method of combining genes from very diverse organisms. It is reasonable to ask, however, what would happen if any of the other methods become equally successful. Will a profusion of guidelines appear? Will one committee oversee all genetic experiments

*For example, antibiotic resistant plasmids have been transferred from *Staphylococcus aureus* to *Bacillus subtilis* across species barriers by transformation, not by rDNA. Foreign genes for the enzyme amylase have also been introduced into *B. subtilis*.

Ethical and moral concerns

The perceived risk associated with genetic engineering includes ethical and moral hazards as well as physical ones. It is important to recognize that these are part of the general topic of risk. To some, there is just as much risk to social values and structure as to human health and the environment. (For further discussion see ch. 13.)

Conclusion

Thus far, no demonstrable harm associated with genetic engineering, and particularly rDNA, has been found, But although demonstrable harm is based on evidence that damage ***has* occurred at one time or another, it does not mean that damage *cannot* occur.**

Conjectural hazards based on analogies and scenarios have been addressed and most have proved less worrisome than previously assumed. Nevertheless, there is agreement that certain experiments, such as the transfer of genes for known toxins or venoms into bacteria, should still be prohibited because of the real likelihood of danger. Still other experiments cannot clearly be shown to be hazardous or readily dismissed as harmless. Hence, a political decision is likely to be required to establish what constitutes acceptable proof and who must provide it.

Given that potential harm can be identified in some cases, its probable occurrence and magnitude quantified, and perceived risk taken into account, a decision to proceed is usually based on society's willingness to take the risk. This triad of the physical *(actual risk)*, psychological (perception of risk), and **political *(willingness to take risk)*** plays a role in all decisions relating to genetic engineering.

The potential benefits must always be considered along with the risks. Decisions made by RAC have reflected this view—e.g., when it approved the cloning of the genetic material of the foot-and-mouth disease virus. The perceived benefits to millions of animals outweighed the potential hazard.

Recombinant DNA techniques represent just one of several methods to join fragments of DNA from different organisms. The current Guidelines do no extend to these other techniques, although they share some of the same uncertainties. Ignoring the consequences of the other technologies might be viewed as an inconsistency in policy.

While the initial concerns about the possibility of hazards at the laboratory level appear to have been overstated, other types of potential hazards at different stages of the technology have been identified. Emphasis has shifted somewhat from conjectured hazards that might arise from research and development to those that might be associated with production technologies. As a consequence, there is a clearer mandate for existing Federal regulatory agencies to play a role in ensuring safety in industrial settings.