"Document Control"

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FROM: GALAS, David J.: DEPARTMENT OF ENERGY

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 12/06/91

SUBJECT: RE: THE BIOTECHNOLOGY PASSBACK FROM OMB. HE LISTS SEVERAL PROBLEMS HE HOPES CAN BE ADDRESSED.

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DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED:

ACTION REQUIRED: DIRECT REPLY

STAFF ACTION:

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SENDER'S DUE DATE:

OSTP DUE DATE: 12/26/91 STAFF DUE DATE

DATE COMPLETED: DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
ENVIRONMENT
Vickie Sutton

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WHITE HOUSE TRACKING #:

CONTACT PERSON:

PHONE: EXT:

REMARKS:

CLOSED

OSTP RECEIVED: 12/12/91 DEPT RECEIVED:

FILE: LIFE SCIENCES-BIOTECHNOLOGY

CENTRAL FILES: Pres

5089

Department of Energy
Washington, DC 20585

6 December 1991

Dear Dr. Bromley,

The Biotechnology Research Subcommittee met this afternoon to consider the biotechnology passback from OMB. In general, we were very pleased with the response to the crosscut proposal and we appreciate the support of the FCCSET office in working with OMB. There are, however, two problems with the biotechnology budget that I would like to bring to your attention.

The most significant problem is the EPA passback for biotechnology (request: $24M; passback: $16M). Although DOE, NSF, and DOC have significant programs in environmental biotechnology, the EPA programs are integral to the national environmental biotechnology program. The EPA program focuses on 1) research related to oil-spill clean-up and 2) environmental diagnostics research, and represents a unique and significant contribution to the overall effort. The EPA passback is not consistent with one of the principal recommendations of the BRS - that more research is needed to capitalize on the major opportunities in environmental biotechnology. The recommendation reads, "The federal investment in biotechnology research related to the environment should be significantly increased and coordinated more closely among the federal agencies." I understand that EPA is appealing this component of their passback. I have attached a summary of further background information for your benefit.

Another problem with the overall passback concerns FDA. A very modest request from the FDA for an increase in their biotechnology research from $35M to $37M was not approved by OMB (passback: $34M). This is an important area for the future of biotechnology commercialization. Pharmaceutical products from biotechnology are rapidly filling the review pipeline. In its role as reviewer of products FDA acts as "gatekeeper" for the passage of products into the marketplace. To properly address the issues of efficacy and safety for this new generation of products, and to provide information for a science-based regulatory process, FDA's research activities in biotechnology should be strengthened. They need to run faster to keep pace with the science Perceived savings here could actually result in some severe costs in the future.

I hope that these concerns can be addressed. I think that correction of these two difficulties would round out a very strong national biotechnology research program to which we are rather proud to have contributed.

Sincerely,

David J. Galas
Chairman,
FCCSET Biotechnology Research Subcommittee

attch: 1
cc: Dr. James Mason, Chair FCCSET, CLSH

BIOTECHNOLOGY RESEARCH: Talking Points

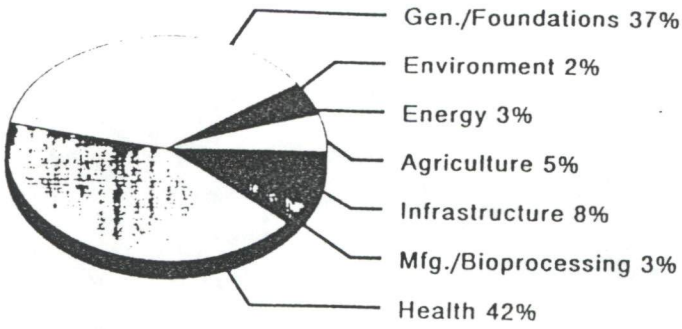
Environmental Situation (Magnitude of Pollution in US Today)

- Over 30,000 hazardous waste sites; over 1200 on national priority list for clean-up; ca. 250 in progress (currently, less than 140 sites are employing bioremediation or have had it suggested as a potential clean-up technology)
- Over 400,000 leaking or potentially leaking underground storage tanks in US; 63,000 are confirmed leaking
- 2.7 billion pounds of emissions reported in fiscal year 1987 for 359 toxic substances in US
- Over one billion pounds (1987 estimates) of chemical pesticides are used in the US annually
- Over 11,000 miles of streams have been polluted by sediment or acid from surface and underground mining combined
- Concern over the loss of biodiversity has become and international issue

Opportunities for Biotechnology to Address Environmental Problems

- Useful adjunct to other cleanup and pollution prevention technologies - (Biotreatment; Bioremediation; Biofilters)
- Creating sentinel organisms that act as continuous monitors of environmental condition in remediation situations (e.g., at waste sites or in constructed wetlands)
- Heavy metal detection (biosensors) and recovery (biosorbent technology)
- Replacement of chemical pesticides with more environmentally acceptable biological pesticides (microbial pest control agents)
- Development of biodegradable materials (biopolymer based plastics; wood/plastic composites)
- Biomass conversion (fermentation of lignin or agricultural feed stocks) for production of petroleum supplements/substitutes (alcohols)
- Facilitate the process of biorestoration at affected sites (e.g., planting metals resistant organisms)
- Environmental diagnostic tools (e.g., biosensors) to provide real time, continuous monitoring in situ

FEDERAL INVESTMENT IN BIOTECHNOLOGY RESEARCH



FY 1992 = $3,644.4M
FY 1993 = $3,946.7M
(Social Impact Not Shown)

SLIDE11

Biotechnology Research at EPA

EPA's Biotechnology Research Goals

- Establish the scientific and technical foundation for the implementation of biological solutions to environmental problems
- Transfer biotechnology research discoveries to environmentally safe commercial applications
- Realize the benefits of biotechnology for protecting and restoring the environment

EPA's Current Biotechnology Research Programs

Biosystems Technology Development/Oil Spills

- Goal: Develop and demonstrate biological treatment systems and bioremediation technology for oil and other pollutants in the environment
- Objectives:
  - Identification, characterization and modeling of biodegradation processes in soil, water, and sediments
  - Development of innovative biological and/or engineering approaches to treatment biosystem design and operation
  - Determine the environmental fate and effects of organisms used in treatment biosystems

- Develop of procedures to mitigate exposure and adverse effects from implementation of biotreatment technology

- Transfer of technology information

Biotechnology Risk Assessment Research

o Goal: To provide the necessary tools for identifying risks and assessing the safety of biotechnology product development, distribution, and use

(Note: Until 1991, when USDA was required to do so, EPA was the only Federal Agency with this type of research program)

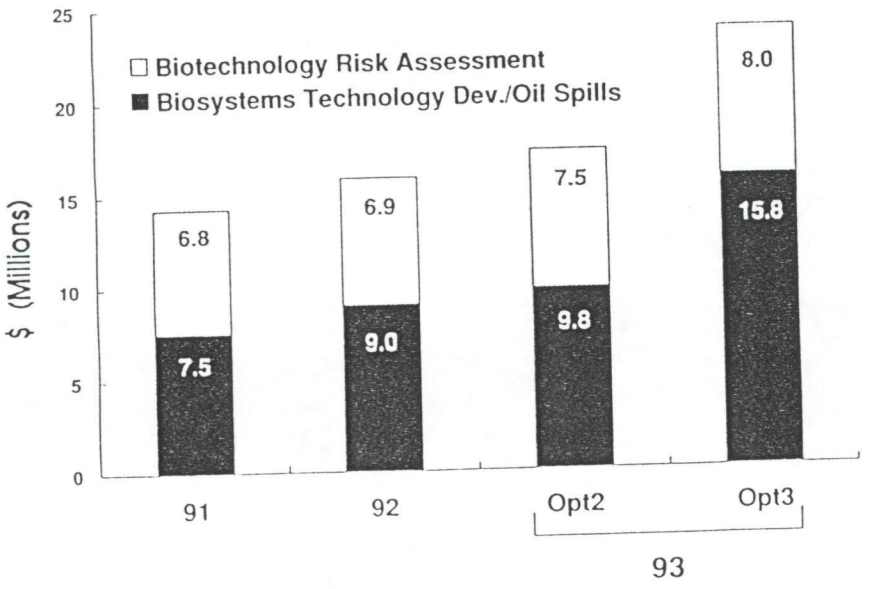
o Objectives:

- Provide basic tools for monitoring microbial survival, movement, and genetic transfer

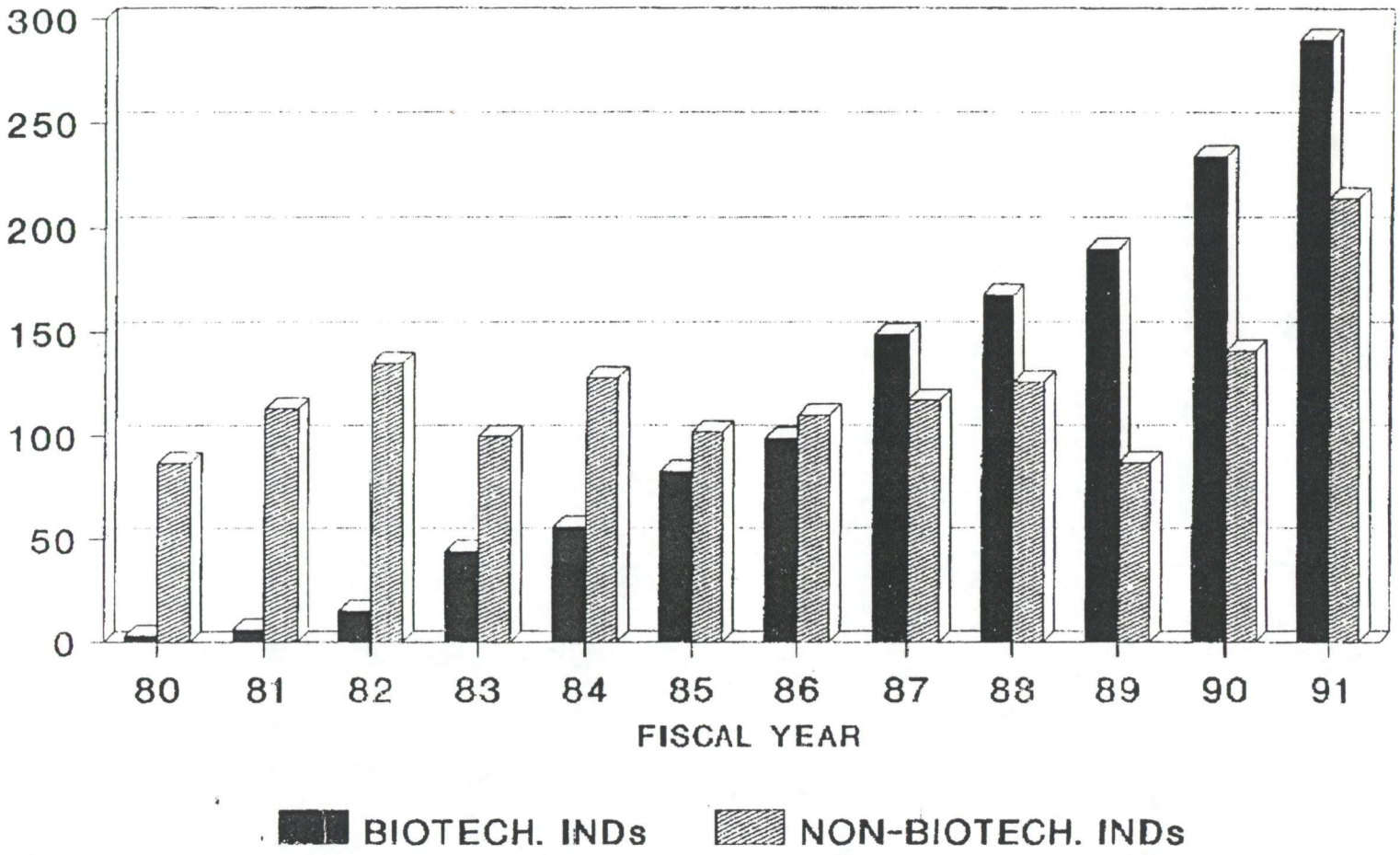
- Develop and test conceptual and experimental frameworks that identify and describe environmental impacts of biotechnology products

- Determine criteria for judging containment and monitoring strategies used to limit or track the dispersal and dissemination of biotechnology products

EPA Biotechnology/Biosystems Research Budgets



BIOTECHNOLOGY GROWTH
Measured in Biologic IND* Submissions



*IND stands for Investigational New Drug Applications

THE WHITE HOUSE

WASHINGTON

December 18, 1991

Dear David:

Many thanks for your letter of December 6 in which you spell out the problems with the biotechnology passback from OMB. I appreciate your identifying the EPA and FDA problems in detail and agree with you that it is important that we try to bring these two agencies into line with the Committee recommendations. I shall see what I can do in that direction.

Let me take this occasion to thank you for the outstanding leadership that you provided in this very difficult task during this past year. I believe that you and your colleagues in the biotechnology crosscut have developed a biotechnology research program of which we, as a Nation, can be proud, and I want to express to you my personal thanks for the enormous effort that I know you personally devoted to the completion of the task in such excellent fashion.

With warmest best wishes,

Sincerely yours,

D. Allan Bromley
The Assistant to the President
for
Science and Technology
and
Chairman, Federal Coordinating Council
for
Science, Engineering and Technology

Dr. David J. Galas
Associate Director
Health and Environmental Research
Department of Energy
Route 270
Germantown, Maryland 20545

159 Willers Lane
Decatur, GA. 30033

Science and Technology Advisor to the President
The White House
Washington D.C.

4/19/91

Greetings:
Since we have a stake in ending the oil fires in Kuwait, I am writing you with a suggestion to pass on to the parties.

Construct an extraordinarily wide and massive mobile "sled", of steel and concrete with modern shuttle-tile ceramic tile or other insulating materials on the underside. The sled will have built into it reservoirs/tanks and high pressure nozzles/pumps for injecting/shooting anti-fire chemicals.
The sled is towed at low elevation or ground contact level to the oil well(s), bulldozing all obstructions in the process. When over the oil well, it will blanket the latter with its massive size, and exude a pressurized blanket of chemicals on the underside, depriving the fire of what it needs. Etc., etc., etc.
Uncommon situations call for uncommon scale of operations. There is no excuse for the piece-meal approach.

F. Paul Bippmann, Eng. Advis.

cc: Senators Nunn, Fowler

"CORRESPONDENCE TRACKING"

TYPE: INFORMATION DOCUMENT NUMBER: 9120842

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FROM: DAVIS, Bernard D,: BACTERIAL PHYSIOLOGY UNIT, HARVARD

TO: DR. BROMLEY

DATE OF CORRESPONDENCE: 03/15/91

SUBJECT: FOLLOW-UP QUESTION TO A RECENT LECTURE CONCERNING EDUCATION OF THE PUBLIC AND LEGISLATORS ON BOTH LONG TERM AND SHORT TERM BENEFITS OF BASIC RESEARCH.

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ASSIGNED TO:

ACTION REQUIRED:

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SENDER'S DUE DATE: OSTP DUE DATE:

DATE COMPLETED:

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COPIES TO: D. Allan Bromley
Life Sciences

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WHITE HOUSE TRACKING #: CONTACT PERSON:

REMARKS: A response is not expected to the question, it is a point which you might find of interest.

DATE RECEIVED: 03/22/91 FILE: P LIFE SCIENCES-BIOTECHNOLOGY

9120842

BACTERIAL PHYSIOLOGY UNIT
HARVARD MEDICAL SCHOOL
25 SHATTUCK STREET
BOSTON, MASSACHUSETTS 02115
TELEPHONE: (617) 732-2022

Mar. 15, 1991

Dr. Allan Bromley,
Office of Science and Technology Policy,
The White House,
Washington, DC. 20418

Dear Dr. Bromley,

Since I am sharing a course on Biotechnology at the Kennedy School of Government with Lew Branscomb and Rollin Johnson I had the pleasure of being invited to the recent dinner in your honor, and I was particularly interested in your lecture. Had there been time for more questions I would have asked the following.

You are no doubt correct in arguing that an appeal for government funds will be more effective if it is based on opportunities for society rather than on the entitlement of scientists. Yet what looks like entitlement is really an appeal for support of basic research directed by curiosity about the world, together with recognition that the success of this enterprise has been multiplying the opportunities for further advances. The main justification for asking for tax money for this purpose is the historical evidence that the most important scientific breakthroughs, including ones with direct social benefits, cannot be predicted but have been the byproduct of such basic research. A striking example is molecular recombination of DNA -- not a single discovery, but the integration of many earlier esoteric discoveries in bacterial and molecular genetics. So the question is: if we emphasize only opportunities, and do not continually try to educate the public and legislators on the long-term benefits of basic research, is there not some danger that the result will be greater pressure on scientists to focus on targeted, short-term goals at the expense of untargeted research?

I do not expect you to take time from your busy schedule to comment on this particular formulation of some obvious ideas. But I thought they might interest you.

I am enclosing some of my recent writings on science and society, which focus especially on problems of the Office of Scientific Integrity and those raised by the Human Genome Project. The latter exemplifies the danger of having funding influenced too much by the understandable preference of legislators for a nice, definite goal -- in this case one of questionable value but great appeal.

I am also enclosing a description of a book that I have organized for the Amer. Acad. Arts and Sciences, for a general

audience, on The Genetic Revolution: Scientific Prospects and Public Perceptions; it is scheduled for publication this summer. A collection of my earlier writings on science and society, Storm Over Biology (Prometheus Books, 1986), deals with earlier controversies over genetic engineering, and more generally with problems engendered by the antiscience movement and by efforts to politicize science. If you are interested I would be happy to send you a copy.

Sincerely,

Bernard D. Davis
Adele Lehman Professor of
Bacterial Physiology,
Emeritus

Some problems with a crash program

BERNARD D. DAVIS

Bacterial Physiology Unit, Harvard Medical School, Boston, Massachusetts 02115, USA

THE HUMAN GENOME PROGRAM (HGP) is directed by a distinguished group of scientists and is supporting much excellent research; nevertheless, it has aroused widespread discontent in the biomedical research community. First, it is thought to be crowding out more productive R01 grants; and although this complaint may become less intense if the R01 crisis is alleviated next year, it will persist. A deeper complaint is that the sense of urgency surrounding the program is not scientifically justified.

Perhaps the deepest problem, however, is procedural. The HGP began, illogically, as a means of expanding the biological activities of the Department of Energy (DOE). NIH was initially reluctant but joined when the project's definite goal – to sequence the human genome serially – proved politically overwhelming, though it was soon recognized as unrealistic and is now postponed. Nevertheless, it is still central in a funding process that reflects the expertise of the DOE in appealing to Congress for large expenditures. This process encourages a good deal of hype. For example, we are told that locating the cystic fibrosis gene cost $120 million – or $60 or $150 – when in fact $120 million is the cost of *all* cystic fibrosis research to date.

The record of allocating funds within science by such lobbying is not reassuring compared with methods that respond to the changing interest of young investigators in promising fields. The premature crash program of cancer research in the 1970s, initiated by pressure from influential laypersons, was not very cost effective. In a more current example, desperate AIDS victims, pressing for ever-expanding research, are clearly not in a position to evaluate the limits of effective funding. But what is novel about HGP is strong lobbying for one field from within the scientific community. Would it be desirable to have a similar push from neurobiologists and immunologists?

The current allocation gives one-third to DOE and two-thirds to NIH, and I am not in a position to evaluate the wisdom of this political compromise. But I would question whether the growth of the overall level of funding has been guided by a proper mechanism. In the appropriation for next year, Congress was evidently influenced by criticisms from some scientists, for it awarded only about half of the 80% increase requested. But next year we will again face the demand for building toward $200 million a year (plus allowances for inflation). This level is not negligible: it might be compared with the current $700 million for the wide variety of fundamental programs supported by the National Institute of General Medical Sciences.

The distribution of funds within the HGP also raises problems, for it seems to be excessively separated from the rest of the NIH granting program. One result is that a person studying a specific gene in *Escherichia coli* is much less readily funded than one who seeks a gene by genome sequencing. Moreover, the explosive growth and autonomy of the HGP, inevitably appears to give a selected group of scientists an improper advantage in funding.

Let us now look at the scientific criticisms that reinforce the concern over procedure. They are mostly directed at the ultimate goal of complete sequencing.

1) To some defenders this goal is an exciting challenge because it is the key to the chemical underpinnings of human nature. But this is a highly personal, esthetic judgment: not all of us wish to climb Mt. Everest. For many the sequence is only a tool and not a profound goal in itself.

2) If the real goal is thus not to catalog but to understand the human genome, by relating sequence to function, how can we best advance it? We have already learned a good deal through a function-based approach: the relatively straightforward procedure of moving from mRNA or a protein, via a cDNA, to its gene and regulatory regions. But blind sequencing, as a means of advancing our understanding, must overcome two obstacles. The problem of the cost of plowing through the "junk" (unfortunately misnamed) to find the interesting regions (ORFs) has been extensively discussed. The other problem is to find where and when the product of such a region works. Experts in the HGP could help the scientific community evaluate their program by presenting a detailed comparison of the scientific advantages and limits of the alternative function-based and sequence-based approaches.

"The record of allocating funds within science by such lobbying is not reassuring compared with methods that respond to the changing interest of young investigators."

3) The sequence-based approach also is clouded by special political and social problems. One is to determine how long its practitioners may withhold a sequence of interest that they have encountered. Others are the prospect of training a large number of scientists on projects that teach them only sophisticated techniques, and the effect of a "big science" atmosphere on the style of biomedical research.

4) Trying to understand the noncoding regions of the genome is a major scientific challenge, but it has received little discussion. The answers will surely emerge from ingenious study of a sample region of some chromosome, rather than by induction from a catalog of the 3 billion bases of all the chromosomes. The bulk of the genome would thus cease being "junk," and complete sequencing would then be much more interesting.

5) Jim Watson asserts that to motivate persons engaged in blind sequencing we must proceed on a scale that promises to reach the complete sequence within a person's lifetime – specifically, 15 years. But it is doubtful that this motivation will be important for most sequencers. Moreover, the goal and the deadline seem artificial. The function-based alternative would proceed step by step, accumulating useful knowledge and unpredictable breakthroughs along the way, and basing expanding support primarily on new, promising leads rather than on a deadline. There is as yet no assurance that the sequence-based approach is better. Indeed, an expanding HGP could even be counterproductive in terms of its own ultimate goal, if it should compete significantly with the

other areas of biomedical science, as these are now almost all revealing new proteins and hence new genes.

For these reasons, and because of the impressive past record of investigator-initiated grants, many biologists oppose large-scale targeting, except for a clearly attainable, immediately valuable goal such as mapping the genome. The most contentious issue is whether complete sequencing should be sought directly or should emerge eventually from expanding study of regions of interest. If the answer is the latter, it would not appear justifiable to invest massive amounts now in research on improving sequencing methods and informatics. To be sure, any advances would also help function-based research, but sequencing is rarely its most expensive step.

With these many questions, and with the resulting tensions in the biomedical research community, those involved might do well to drop their focus on complete sequencing, with its artificial deadline. The scale of funding of the HGP, and the need for centralized administration, would then have to be justified in terms that would be comparable to the rest of biomedical research: the present or foreseeable return from its current activities. FJ

How Far Should Big Brother's Hand Reach?*

The mandate of OSI and OSIR may lead to government interference in research

BERNARD D. DAVIS

Someone has suggested that the invention of peer-reviewed grant applications was the most original contribution of our country to civilization. Certainly this mechanism for bypassing hierarchy in the support of research and for encouraging independence at an early age deserves a great deal of credit for the spectacular success of the biomedical sciences since World War II. And credit also goes to the National Institutes of Health (NIH) for developing an effective, mutually respectful relationship with its extramural constituency, depending on study sections to evaluate quality, and allowing the grantee great freedom in the conduct of the research.

Against the background of this happy and effective relationship, recent congressional investigations have generated the impression that our biomedical research enterprise is now suffering from a crisis of integrity. Though this impression is greatly exaggerated, it is built on the fact that research institutions or NIH has often failed to respond adequately to allegations of fraud in research. The mechanisms for dealing with this problem do need improvement.

The answer from the Public Health Service (PHS) has been to establish an Office of Scientific Integrity (OSI) in NIH and a supervisory Office of Scientific Integrity Review (OSIR) in the Department of Health and Human Services (HHS). Unfortunately, the mandate of these two offices goes beyond investigating fraud, and it raises the prospect of growing involvement of the government in other aspects of the conduct of research. This prospect surely deserves close attention from the scientific community.

Bernard D. Davis is an emeritus professor at Harvard Medical School.

*This article is based on a presentation by Bernard D. Davis at the President's Forum, sponsored at the 1990 ASM Annual Meeting by New Brunswick Scientific Co.

Increased Recognition of Fraud in Research

Since the events leading up to the development of the new offices have been widely publicized, I will comment on only a few features.

First, because scientific research is conducted by human beings, occasional fraud is not new, and it remains inevitable. Moreover, various changes in our general culture and in the culture of science may well have led to some increase. This possibility seems to be supported by the fact that OSI at NIH is currently investigating 80 allegations—and past experience suggests that perhaps a third of those will prove to be justified. Even if many of these represent an accumulated backlog now released by a changing climate, the number is probably larger than most scientists would expect.

Nevertheless, there is no base line that allows us to know whether fraud has increased in frequency or only in recognition in recent years. But even if there has been a real increase, a more important question is its impact on the overall progress of science. This cannot be substantial, or else the current explosion of advances would not be possible. Moreover, against the background of 24,000 grants supported by NIH, the current 80 allegations in OSI, and perhaps 30 real cases, represent a level of cheating to which Congress—and even the clergy—might aspire.

But even though there is no crisis, the problem is one of deep concern to scientists, and it deserves more attention than our trusting community has generally given it. Scientists, dependent on one anothers' data, have more reason than anyone else to wish to minimize fraud. Unfortunately, scientists and legislators tend to mistrust each other's approaches. Legislators find it politically attractive to assert the virtuous though unattainable goal of extirpating fraud, root and branch, at all costs. Scientists, accustomed to dealing with science as an imperfect, highly error-

prone, self-correcting process, are more concerned with balancing two goals: the need to discourage and punish fraud, on the one hand, and the need also not to introduce an atmosphere that would damage an extraordinarily successful enterprise.

Scientists, dependent on one another's data, have more reason than anyone else to wish to minimize fraud.

The hearings on the issue by Rep. John Dingell provided an extreme example of congressional zeal. He began by legitimately pursuing several established cases, but he then violated any sense of fairness by tarring David Baltimore with the implication of fraud in an unsettled dispute, which should never have been examined in the one-sided "court" of a congressional hearing. The Public and Scientific Affairs Board and the Council of ASM severely criticized this procedure, as did the Public Affairs Advisory Committee of the American Society of Biochemistry and Molecular Biology, which I then chaired. I will not comment in detail on this well-known episode, but I will note that the resulting public discussion led to a good deal of exposure of the public to several unfamiliar aspects of science, with perhaps some benefits.

First, the public probably acquired some clarification of the misconception of science as a method that should guarantee error-free results: error is inevitable, and so it must be carefully distinguished from fraud. A second, much muddier issue was aroused by the suggestion (unfortunately not yet dead) that the problem could be solved by random inspection of notebooks—as though scientific notes could be treated much like account books, in which the credits and the debits can be traced to their sources and must come out equal. Finally, there has probably been little clarification of a third issue: the misconception that the tradition of science requires correction of every error in the literature. Traditionally, only important errors, on which colleagues are likely to try to build, are corrected, while the others are bypassed and left to rest in obscurity.

Fear of Draconian Legislation

The wide publicity given to the Dingell hearings, coupled with his reputation as an exceptionally powerful legislator, created deep anxiety among those in Washington concerned with the administration of science. It led to three unofficial steps that preceded establishment of the new offices.

First, the Association of American Universities and the Association of American Medical Colleges undertook a major rewrite of an earlier joint pamphlet, with the purpose of offering research institutions a better framework for setting up formal policies and practices for responding to allegations of fraud. This document urged that the first response be a confidential initial inquiry, followed by an open investigation only when justified by the results of the inquiry. The document emphasized the need to protect the rights of both the whistleblower and the accused and the need to preserve an atmosphere conducive to the practice of creative science. I had an opportunity to participate in the final framing of this booklet, which we hoped would be seen to meet the need and would keep the responsibility for improving the responses in the hands of the research institutions. In any event, however, this proved to be a vain hope.

Second, the Institute of Medicine of the National Academy of Sciences set up a committee that produced the report *Responsible Conduct of Research in the Health Sciences*. While agreeing that it was important to try to keep fraud to a minimum, this document emphasized that such violations of the canons of science are far less frequent and hinder the progress of science far less than what might generally be called "sloppiness." The report went on to analyze in detail a variety of practices that fell under this heading.

I agreed thoroughly with this part of the document, with one exception. It failed to analyze, or even to note, the obviously greater frequency of the problem in clinical research (in which it can also have more serious consequences) than in the basic biomedical sciences. On the contrary, the report universalized the problem by suggesting that the committee's recommendations might also be useful for physicists and chemists.

Unlike the predominantly satisfactory analysis, the recommendations that followed seem to me to have presented a serious problem. The main theme was that the government should require applying institutions to develop formal practices to promote high quality and discourage sloppiness in research—for example, courses on research ethics. The committee attempted to protect the autonomy of the academic institutions by asserting that they, not the government, should retain the ultimate responsibility. On the other hand, if the government did not find the actions of an institution adequate, it should reject all of its grant applications. This seems to be a politically naive way of trying to preserve autonomy.

I found it hard to understand why an academic group would invite such direct and even forceful government intervention in the conduct of research. However, when I sought clarification from a member of the committee, he stated that the National Research Council staff briefing the committee had painted a dire picture: unless the committee's recommendations to research institutions were sufficiently forceful and detailed, there was grave danger that Congress would set up its own mechanism for policing science. This presumption clearly had a large impact on the report, and it seems reasonable to suspect that the resulting invitation from the academic community encouraged

the broad mandate of the offices that were subsequently set up by PHS.

In a third, smaller development, NIH contributed to expansion of the role of government by introducing a terminological change. Its lawyer insisted that fraud—the term generally used until then—had a technical legal meaning that did not apply to falsification of data, and so the problem should be redesignated misconduct. I have subsequently found that not all lawyers agree with this narrow conception of fraud. In any case, the Public Affairs Board of the Federation of American Societies for Experimental Biology (FASEB) strongly opposed the term misconduct as being too open-ended.

FASEB also opposed another change proposed by NIH: that the definition of misconduct include not only falsification, fabrication, and plagiarism but also "practices that deviate seriously from those generally accepted." This extension could create obstacles to eccentric, highly original research, though that was clearly not the intention.

Despite vigorous arguments by the president of FASEB, Howard Schachman, our organization lost the battles on both the use and the definition of the term misconduct. As we shall see, this terminology, used in establishing the two offices, has already had an effect.

The Two New Offices

The function of OSI is primarily to monitor any investigations of misconduct being carried out in research institutions and to conduct its own investigations as necessary. OSIR makes policy, reviews the investigations, and decides on the steps to be taken when wrongdoing is established. OSIR thus gets HHS directly into decisions on specific interactions with grantees. This is a novel precedent, for ordinarily the director of NIH reports to HHS on matters of policy, while in its specific interactions with scientists, NIH is quite autonomous.

The establishment of OSIR is readily understood as an effort to satisfy legislators who doubted the ability of NIH to police itself. Several considerations, however, suggest that this office may not be a necessary one, and it may even be a source of problems.

(i) It wastes both money and time to set up two offices to divide a function that could well be performed by one.

(ii) The very limited authority of OSI, unable even to rule on the disposition of the cases that it handles, makes its directorship much less attractive at a time when it would seem desirable to have the traditions of this fledgling office initiated by a distinguished senior scientist who would bring wisdom to its delicate operations. In the long run, such a limitation on OSI could be counterproductive to the very purpose of the two offices.

(iii) In our present search for the best way to discourage and punish fraud without discouraging creative research, NIH can build on wide connections with and respect from the scientific community. HHS is likely to be seen as more distant from and less sensitive to the needs of the scientific enterprise. To those who see the solution in terms of a police action, this separation may seem desirable, but it is unlikely to help advance science.

(iv) NIH is plagued with organizational problems, as shown by the extraordinary difficulty it has had in searching for a new director over the past year. These problems stem in part from the lack of sufficient authority in that position. The director has to act through HHS on all matters of policy, even though NIH is a much larger operation than the more autonomous National Science Foundation. Making OSI subservient to OSIR adds a small, irritating handicap to NIH.

In the light of these considerations, it would appear desirable to have the structure of the two offices reviewed after the issue of scientific fraud has cooled down.

Quality versus Fraud

Meanwhile, I would like to focus on a potentially much more serious aspect of the charter of OSI. Not only will this office monitor and conduct investigations, it also has an extra mandate to "promote high standards of laboratory and clinical investigations in science through a prevention and education program." This phrase is fraught with possibilities for expanding governmental interference in the conduct of research.

My concern over this very broad charter led me to publish a short article in *Science* (**246**:736, 1989) stating that with this extra mandate the law has crossed the critical line between fraud and matters of scientific judgment. In response (Letter, Science, **247**:144, 1990), James O. Mason, assistant secretary for health in HHS, and Lyle W. Bivens, acting director of OSIR, defended a catalytic role of the PHS offices in fostering the development of standards for research conduct. Moreover, they stated, there are no immediate plans for implementing the Institute of Medicine proposal that institutions receiving PHS grants be required to institute formal policies and procedures in this area. This reply seems very reassuring.

The government already has strong and appropriate leverage over quality through the granting mechanism.

However, the reassurance may be only temporary, for the same paragraph ended with the statement that the response of institutions will demonstrate whether there is a need for more formalized requirements. Moreover, as was noted in my rebutting letter (Science, **247**:145, 1990), it is clear that those currently responsible for OSIR do not regard the extra mandate as simply a hypothetical activity designed to reassure Congress but unlikely to be implemented. Their letter first justified the interest of their office in "high stan-

dards of conduct," a term that could be acceptable if it clearly meant the opposite of misconduct. However, later the discussion subtly shifted to "high standards of investigation"—i.e., quality.

This is the heart of the problem. The government already has strong and appropriate leverage over quality through the granting mechanism. In addition, it can legitimately investigate and punish fraud. But the more borderline kinds of "misconduct" in research and publication, including carelessness, bad judgment, and improper distribution of credit, are another matter. It has been the responsibility of teachers, referees, editors, department chairs, appointment committees, and granting committees to discourage such behavior and to reward high standards. The recent discussions have no doubt raised consciousness of these problems in a useful way. But I doubt that many scientists believe it would be helpful for the government, however good its intentions, to try to deal more directly, or to tell the institutions how to deal, with these fuzzy problems of poor quality. The problem is quite analogous to the line between the role of the law and that of morality in our personal lives. Police are no more appropriate, without a warrant, in the laboratory than in the bedroom—even when tax money supports the inhabitants.

Conclusions

Two general conclusions seem to follow from this exposition. The first is that scientific investigation is inevitably a very imperfect process. We all wish to promote honesty and quality, but we will not be able to eliminate all deviations. A punitive mentality that tries to do so can have a very destructive effect on the atmosphere required for creativity—an atmosphere that should encourage skepticism and flexibility rather than adherence to rigid rules, and playfulness, fun, and pride in achievement rather than defensiveness. Moreover, even within the universities, as President Donald Kennedy of Stanford has emphasized, the regulatory power of the institution is very limited, and we must discourage vigilantes. The attention given to the issue in recent years should encourage preceptors to discuss research ethics explicitly with their students. But indoctrination sessions required by the government might end up much like the boring weekly sessions on dialectical materialism forced on science students in Marxist countries.

The second lesson is the importance of drawing a sharp line between problems of fraud and problems of quality. The letter from the PHS officials suggested the need to refine further the definition of misconduct. However, the refinement seems to move mostly in the direction of further extensions rather than in sharpening the limit, as I am recommending.

At the recent Annual Meeting of ASM, at which I presented this paper at the President's Forum, Suzanne Hadley, former acting director and now deputy director of OSI, emphasized the desire of that office to relate to the scientific community through partnership rather than through oversight. This is very reassuring. But one problem with government involvement in traditionally autonomous aspects of science is that Big Brother's hand reaches through a long and strong chain of command. The person dealing with the scientists in a case may be sensitive to one set of issues, while the inspector general, at the other end of the chain, may have an altogether different set of priorities. Indeed, it appears that the latter are already being put into practice. We were told at the meeting that programs receiving training grants must now provide a formal course in research ethics—and this requirement was initiated by the inspector general, not OSI. Evidently, what I have called the extra mandate of OSI has already grown past the stage of teething.

It therefore seems important to note that at another session at the meeting, the recently appointed director of OSI, Jules Hallum, suggested that the definition of misconduct should be broadened to include sloppiness, because cutting corners is just as irresponsible as cheating. It now appears that this suggestion has been withdrawn. Nevertheless, the proposal illustrates the reasons for my concern over the steps that have eroded the boundaries of the government's original interest in fraud. The desire to make OSI an interesting educational office and not a police headquarters is understandable and, in principle, commendable. But an educational role of the government in the highly personal conduct of research, however well-intentioned, will always have dangers, because the very nature of government makes it difficult for it to avoid a heavy hand.

We must also recognize the danger that such invasions of the autonomy of scientists, already begun, may grow. I would therefore urge interested members of ASM to convey their views on this subject to Dr. Hallum and to the acting director of NIH, William Raub. □

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~~Draft for~~ NIH Alumni Association Newsletter 3/4/91

Zeal in the Office of Scientific Integrity

Bernard D. Davis

Since administrators wish to protect their institutions from embarrassment, it is not surprising that they have often been reluctant to respond to allegations of fraud in research. We are now paying a price, as congressional investigations have led to exposure of a substantial number of cases of fraud -- more than most scientists would have expected. The increase might only reflect better detection -- though it would not be surprising if the frequency had also risen, since standards of integrity have declined conspicuously in our culture (including the highest levels in our government). Nevertheless, the recognition of a few dozen cases of fraud, among the 24,000 grants supported by the NIH, does not seriously undermine confidence that the great majority of scientists have extreme concern for scientific integrity, on which their whole enterprise depends.

While this confidence seems to be generally shared by scientists, some legislators have evidently been convinced of a more serious crisis in science. In response to their criticism the Department of HHS established two new offices: the Office of Scientific Integrity (OSI) in the NIH, and a supervisory Office of Scientific Integrity Review (OSIR) in the Department. The latter office not only sets policy but also makes the final decision on the investigated cases.

Since these new offices may significantly affect the future style of research and the relations between scientists and the

NIH, they deserve close scrutiny. I shall discuss three aspects of the problem: the effects of dividing the responsibilities between two offices; their very broad mandates; and the zeal of their present administration.

On the matter of structure: while it was obviously necessary to strengthen the mechanisms at the NIH for dealing with fraud, the existence of two offices, for a function that could well be performed by one, wastes both money and time. Moreover, the more elaborate the offices, and the machinery that they require in research institutions, the greater the expenditure. Indeed, since the initial Congressional inquiry into fraud was based on the legislators' obligation to prevent waste of taxpayers' money, it would be interesting to compare the cost of the present extensive machinery and activities with the savings.

In addition, if mechanisms for dealing with fraud have the goal of improving the research enterprise, they will not be effective if they are simply imposed as a policing action; they must have the cooperation of the concerned scientific community. The HHS office, lacking the broad connections of the NIH with that community, seems unlikely to be helpful in achieving this goal.

A final comment on the structure of the offices: subordinating the OSI to the OSIR makes the position of its Director less effective and less attractive. Moreover, this decision further diminishes the waning authority of the Director of the NIH -- an unfortunate trend in recent years, whose negative impact on the attractiveness of that office and on the

status of the institution is widely recognized.

More important than the structure of the new offices is the second problem, their broad mandate. The groundwork was laid early in the discussions of fraud, when the NIH insisted, on debatable legal grounds, that the term "fraud" must be replaced by "misconduct." Moreover, this term was defined to include not only falsification, fabrication, and plagiarism, but also "practices that deviate seriously from those generally accepted." The Public Affairs Board of FASEB vigorously opposed the change, on the grounds that the term misconduct, and even more the concept of generally accepted practice, are too open-ended in this context. But we lost. Somehow the old-fashioned term "dishonesty" never got into the act. As George Orwell has taught us, language is important in politics -- and "misconduct" has turned out to be an invitation to an ever-expanding scope of government involvement.

The resulting mandate charges the new offices not only with monitoring and conducting investigations of misconduct: they should also "promote high standards of laboratory and clinical investigations in science through a prevention and education program." This phrase is fraught with possibilities for encouraging the government to mix problems of misconduct with problems of quality in the conduct of research. And even though the government may enter this area with the wish to be a beloved teacher in a noble cause, its structure inevitably makes its hand heavy.

This is the heart of the problem. The government already has strong and appropriate leverage over quality through the

granting mechanism. In addition, it can legitimately investigate and punish fraud. But it is another matter for the government to become involved in pursuing less weighty (and more widespread) faults of scientists, such as carelessness, bad judgment, and improper assignment of credit. The need to discourage such behavior and to reward high standards is important, and it is a constant challenge -- without expectation of perfect success -- to the scientific community, including teachers, referees, editors, department chairs, deans, appointment committees, and granting committees. Moreover, we must concede that recent public attention has been useful in raising consciousness of our need to do better.

Nevertheless, because these problems are inevitably fuzzy and permeate research it seems extremely doubtful that they can benefit from rigid governmental regulations. In our legal system the police require a warrant before they can enter; and without it their presence is no more appropriate in the laboratory than in the bedroom -- even when tax money supports the inhabitants.

My third concern is that the broad mandate of these offices is now being pursued with excessive zeal, rather than with restraint. This was originally only a theoretical possibility, but it is now an actuality. NIH training grants already require institutions to provide formal courses in research ethics; and while it is clearly desirable for preceptors to set examples and to engage in discussions that expose their trainees to the canons of ethical scientific behavior, obligatory courses may bore students of science, much like obligatory courses in Marxism in

some other countries.

An even larger expansion of government intervention is envisaged by by the recently appointed Director of OSI, Jules Hallum: at the annual meeting of the American Society of Microbiology last May he suggested that the definition of misconduct should be broadened to include sloppiness, because cutting corners is just as irresponsible as cheating. Moreover, a subsequent PHS document (8/1/90), describing the policies and procedures of the new offices, provided a further innovation: in addition to their own personnel they will require each PHS agency, and each fund-granting component, to designate a Misconduct Policy Officer. Since the OSI should have no difficulty in receiving information about grantees of any branch of the NIH, one must wonder whether the additional branch officers are needed as conduits for such information or are also expected to initiate searches for misconduct.

I conclude that the new offices have become grotesque, in their evident aim of purifying science root and branch, without recognition that the cure could do more harm than the disease. This threat to science would seem to merit thorough reevaluation of the offices. Nevertheless, the scientific community has not reacted vigorously. However, a recent lawsuit by a defendant against the OSI has drawn attention to the problem, in a way that should promote further discussion. The judge scathingly criticized the process by which the new offices established major new policies and procedures, without public review (Science 251:508, 1991).

This judgment will presumably result in publication of

proposed policies in the Federal Register, inviting public comment. But this contribution of the law, with its traditional emphasis on procedure, will not solve the problem unless the substantive issues elicit comments from scientists on a large scale -- whether in response to that publication or through other connections. The main issue is, of course, the need to balance pursuit of fraud with the preservation of an atmosphere that will continue to encourage creativity and boldness in research.

Though the NIH enjoys a respected and even affectionate relationship with the scientific community, it has not always been courageous in defending principles against political pressures. In an earlier era of red-baiting it refused (unlike some other government agencies) to award grants to such distinguished scientists as Linus Pauling and Elvin Kabat, because they were accused (without trial) of political misconduct. To be sure, that shameful action of the NIH does not provide a strong analogy for the OSI and OSIR, since it was based on phantoms, while these offices are addressing real problems. Nevertheless, their overreaction to political pressure is similar -- and it threatens the welfare of science on a much broader scale.

Government and Quality in Science

BERNARD D. DAVIS

In the mid-1970s the scientific community succeeded in averting the threat of rigid, legislative control of recombinant DNA research. Recently a similar threat has arisen (though with much less public anxiety) over the issue of fraud in science. While Congress has exaggerated the problem, it has been justified in criticizing the weak responses of some of our institutions. In fact, scientists have even stronger reasons than legislators to wish to deter fraud—while also protecting the atmosphere responsible for the current spectacular biomedical advances. For this purpose two academic associations jointly prepared an excellent set of guidelines (*1*). Nevertheless, some scientific organizations have overreacted to the intimidating atmosphere created by some congressional hearings, and they have expanded the problem by inviting the government to be involved with style in science as well as with fraud.

In the first step in this direction, a lawyer at the National Institutes of Health insisted on replacing the term "fraud" by "misconduct." This vaguer term is troublesome. If we have to use it, we should agree that it refers only to falsification and to plagiarism; misconduct should not casually fold in questions of quality or of error.

This overlap has already appeared, in the charter of two new offices: an Office of Scientific Integrity (OSI) within NIH (which is clearly needed) and an Office of Scientific Integrity Review at the Department of Health and Human Services. Their specifications include "promoting high standards of laboratory and clinical investigations in science through a prevention and education program." The law has thus crossed the critical line between fraud and matters of scientific judgment. And even though the recently announced rules for the new offices have defined misconduct appropriately, and have not addressed the issue of quality, the presence of that charge to the new offices, and their need to placate Congress, may yet tempt them to become involved in increasingly detailed management of the practice of science.

A report of the Institute of Medicine (IOM) encourages this temptation (*2*). It described very well a number of "sloppy" practices, including hasty or fragmented publication, honorary authorship, rewards for volume rather than for quality of publication, and inadequate supervision of trainees. It concluded, very reasonably, that these practices are more prevalent and cause more harm to science than outright fraud. However, the recommended solutions raise serious questions.

In particular, the report requested a special NIH office to encourage institutions to ensure high standards in research by developing appropriate mechanisms, including formal instruction in research ethics and monitoring of the supervision of trainees. Although the report emphasized that the institutions should be responsible for specifying and enforcing the mechanisms, it also would give teeth to the "encouragement" by the NIH office: only institutions that had developed such procedures could submit grant applications.

The intent of the IOM committee, to raise standards and to retain the ultimate responsibility within the universities, is admirable. But the proposed role of the government seems politically naive: to make institutions do what they wish, as long as they do something. The report also failed to discuss possible costs of the new bureaucracies—for example, in tensions between faculty and administration, in increased research overhead, and in further discouraging students from entering careers in science.

Scientists deal with problems of quality all the time and in many capacities. And they are aware that Congress and the public are concerned about how well their community conducts itself. We need now to allow this community to respond to this heightened awareness.

It might also be useful to search for the deeper roots of the problem—for example, to examine the cultural patterns that have made sloppiness and fraud much more prominent in some fields than in others, and—even more—to examine our pattern of funding. For while this pattern has advanced research remarkably, it has also created an army of dependents, who derive primary income as well as research support from their grants and are increasingly insecure as the level of funding has become excessively unstable. With many truly excellent investigators under desperate pressure to renew grants, the pressure to cut corners is bound to grow.

In addition to trying to dig beneath the surface of the problem, scientists should help the public to understand that the term "science" covers many kinds of activities. Routine analyses may follow prescribed standards, but the challenging search for hidden truths is unpredictable; it inevitably involves errors; and it requires the same kind of freedom as art. It also requires that scientists be sensitive to abuses of that freedom. Science is an imperfect but phenomenally successful process, and it would be tragic if well-intentioned reactions to its imperfections, or to public misconceptions, should impose constrictive standards (*3*).

Adele Lehman Professor of Bacterial Physiology Emeritus, Harvard Medical School, Boston, MA 02115, and former chairman of the Public Affairs Advisory Committee of the American Society of Biochemistry and Molecular Biology.

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2. Institute of Medicine, *The Responsible Conduct of Research in the Health Sciences* (National Academy Press, Washington, DC, 1989).
3. I thank H. Schachman and R. Schimke for helpful comments.

Letters

cientific Integrity

The Policy Forum "Government and uality in science" by Bernard D. Davis (10 lov., p. 736) expresses concern that the ewly established offices in the Public lealth Service (The Office of Scientific In-grity and the Office of Scientific Integrity eview) will "become involved in increas-ngly detailed management of the practice of cience." In Davis' view, such a concern rises from the stated role of these offices to romote high standards of scientific con-uct, which he interprets to mean that the ffices will be dictating on matters of scien-fic judgment or quality, rather than limit-ng their activities to scientific misconduct.

The promotion of responsible scientific onduct is a responsibility shared by the scientific community at large, grantee and pplicant institutions, professional and aca-lemic associations, and all Public Health ervice (PHS) components supporting re-

earch. It is entirely appropriate that the HS offices will play a catalytic role in ostering the development of standards for esearch conduct. A successful collaboration etween the federal and the scientific-aca-lemic communities in developing such stan-lards is the best protection against regula-ory or legislative remedies.

There are no immediate plans to imple-nent the Institute of Medicine proposal for equiring institutions receiving PHS re-earch grants to have policies and proce-lures to encourage responsible research practices (*1*). It should be noted however hat the recently issued "Final Rule" (*2*) requiring institutions to have policies and procedures for inquiring into and investigat-ing scientific misconduct concludes with a statement that institutions "shall foster a research environment that discourages mis-conduct. . . ." It is the response of institu-tions that will demonstrate whether there is a need for more formalized requirements for prevention and education activities.

The existing peer-review process is the forum for judgments about the quality of research. However, it is important for the Office of Science Integrity and the Office of Scientific Integrity Review, in collaboration with the scientific community, to do a better ob of spelling out what is unacceptable scientific behavior. The limitation of the definition of scientific misconduct to only falsification and plagiarism, as proposed by Davis, would miss a range of unacceptable behaviors that have already been judged by scientific investigative panels to constitute misconduct. Standards for the responsible conduct of science should include the clear-est possible statements of what is unaccept-able behavior, which requires a further elab-oration, not limitation, of the definition of scientific misconduct. A refined definition of scientific misconduct would not "casually fold in questions of quality or of error," as Davis fears, but would in fact serve to more clearly separate differences in scientific judg-ment or honest error from misconduct.

The establishment of the Office of Scien-tific Integrity Review within the Office of the Assistant Secretary for Health provides a vital PHS-wide oversight role for scientific integrity activities and indicates the impor-tance placed by the Department of Health and Human Services on dealing with scien-tific misconduct. We fully intend to contin-ue working with the scientific and institu-tional communities in discussing such im-portant issues as where responsibilities are properly vested for promoting the responsi-ble conduct of research and the proper form of standards and guidelines to foster integri-ty in science.

JAMES O. MASON
Assistant Secretary for Health and
Acting Surgeon General,
Department of Health and Human Services,
Public Health Service, Washington, DC 20201
LYLE W. BIVENS
Acting Director,
Office of Scientific Integrity Review,
Office of Assistant Secretary for Health,
Department of Health and Human Services,
Rockville, MD 20852

REFERENCES

1. *The Responsible Conduct of Research in the Health Sciences* (National Academy Press, Washington, DC, 1989), p. 25.
2. "Responsibility of awardee and applicant institutions for dealing with and reporting possible misconduct in science," *Fed. Reg.* **54** (No. 151), 32446 (8 August 1989).

Response: I am delighted by the comments of Mason and Bivens reassuring us that the new federal offices concerned with scientific integrity do not plan at this time to require formal institutional efforts to encourage responsible research practices. Nevertheless, the authors do not accept the proposal, in my article, that the government should draw a sharp line between fraud (that is, fabrication and falsification of data) and other undesirable practices.

When the rather open-ended word "misconduct" began to replace "fraud" and "plagiarism," President Howard Schachman of the Federation of American Societies for Experimental Biology, and its Public Affairs Committee (of which I was a member), opposed the shift. We obviously lost the battle, and my Policy Forum did not aim at trying to renew it. But the letter from Mason and Bivens illustrates the problem that the shift created: the government is still seeking the precise definition that the law needs. The search is difficult, because the term merges into questions of judgment and quality. For example, the present definition includes "practices that deviate seriously from those that are commonly accepted within the scientific community"—a definition that seemed to our committee far too loose.

The comments by Mason and Bivens further understate the danger of excessive governmental involvement by describing the role of the new offices as promoting "high standards of scientific conduct"—a phrase that would seem to contrast proper conduct with misconduct. But the charter for these offices assigns them a rather different responsibility: promoting "high standards of laboratory and clinical investigations in science through a prevention and education program." This phrase, which clearly gets beyond misconduct into the area of quality, was the main cause of my concern, and it still is. While it is gratifying that the current officials in charge evidently have no intention to delve into this area, a later official might feel obligated to follow the letter of the law. This charge to the offices therefore deserves reevaluation.

We are dealing here with a gray area—and the lighter the shade of gray, the more difficult it is for the government, however laudable its intention to serve as a catalyst, to avoid imposing a rigidity that would do more harm than good. I certainly agree with Mason and Bivens that government as well as scientists and their organizations share responsibility for promoting responsible conduct; but it does not follow that all these groups share the whole range of responsibilities implied by this broad term. Mason and Bivens recognize that the scientific community has a role in determining where responsibilities are properly vested. We will no doubt need continual discussion to ensure that the proper lines are maintained. Because of the intensely personal nature of scientific research, and because students learn standards from the behavior of their preceptors and colleagues, just as children do from their parents and their other contacts, the discussion will always face an ancient and general problem: where should the law end and personal morality begin in setting standards of conduct?

In justifying their position, Mason and Bivens note that "scientific investigative panels" have judged misconduct to include a range of unacceptable behaviors beyond falsification and plagiarism. To my knowledge, the most prominent support for this view (and hence the main focus of my article) was the report of the Institute of Medicine (IOM). I would therefore emphasize that the many researchers with whom I have discussed the matter uniformly disagree with the IOM recommendations. Even though such issues as carelessness, bad judgment, and improper distribution of credit are perpetual problems in science, few scientists seem to believe it would be helpful for government to try to prevent them.

BERNARD D. DAVIS
Bacterial Physiology Unit,
Harvard Medical School, Boston, MA 02115

24.5.1 Evolutionary principles and the regulation of engineered bacteria

BERNARD D. DAVIS

Bacterial Physiology Unit, Harvard Medical School, Boston, MA 02115, U.S.A.

Symposium Editor: L. Siminovitch

DAVIS, B. D. 1989. Evolutionary principles and the regulation of engineered bacteria. Genome, **31**: 864–869.

The introduction of engineered bacteria to the environment is being overregulated, on the basis of several assumptions: (*i*) the danger from deliberate introduction on a large scale is much greater than that from accidental release; (*ii*) the more distant the source of the DNA the greater the risk; (*iii*) novel organisms are likely to cause unexpected ecological damage, like that seen with native organisms transplanted to a novel location; (*iv*) even if the probability of harm is very small, great care must be taken because the harm might be large; (*v*) products of recombinant DNA must be treated differently from products of classical gentic manipulation; and (*vi*) our unlimited power to manipulate DNA implies an unlimited power to refashion organisms. Evolutionary principles contradict all these assumptions. Moreover, our increased power of genetic manipulation must be recognized as an expansion of the biotechnology of domestication; and unlike the physical technologies, the long history of domestication has not adventitiously created harmful by-products. I propose that in dealing with such novel and unpredictable developments it would be better to respond with speed and resilience to problems as they arise, rather than to hamper advances by clumsy regulations based on unsubstantiated guesses.

Key words: bioengineering, antiscience, biotechnology, risk assessment.

DAVIS, B. D. 1989. Evolutionary principles and the regulation of engineered bacteria. Genome, **31** : 864–869.

L'introduction dans l'environnement de bactéries modifiées par génie génétique est surréglementée sur la base de nombreuses suppositions : (*i*) le danger d'une introduction délibérée sur une grande échelle est plus grand que celui d'un échappement accidentel; (*ii*) plus la source d'ADN est distante, plus le risque est grand; (*iii*) il est possible que les nouveaux organismes puissent causer des dommages écologiques inattendus, comme ce qui a été observé lorsque des organismes indigènes ont été transplantés dans des lieux nouveau; (*iv*) même si la probabilité d'un dommage est très faible, il faut être très attentif car le dommage pourrait être très grand; (*v*) les produits d'ADN recombinant doivent être traités différemment des produits de manipulations génétiques classiques; et (*vi*) notre capacité illimitée de manipuler l'ADN implique une capacité illimitée de refaçonner les organismes. Les principes évolutifs contredisent ces suppositions. Bien plus, notre capacité accrue de manipulation génétique doit être reconnue comme une expansion de la biotechnologie de la domestication et, contrairement aux technologies physiques, la longue histoire de la domestication n'a pas créé de sous-produits dangereux de façon adventive. Je propose donc que, pour le traitement de tels développements nouveaux et imprévisibles, il serait préférable de traiter les problèmes rapidement et vigoureusement à mesure qu'ils se présentent plutôt que d'empêcher le progrès par des règlements gênants basés sur des suppositions non appuyées par des faits.

Mots clés : génie génétique, anti-science, biotechnologie, évaluation des risques.

[Traduit par la revue]

Background

The antiscience movement

Although research on recombinant bacteria initially caused deep concern, after this wave receded it appeared that fear of these organisms would no longer interfere with the uses of this powerful methodology. However, the proposed introduction of genetically engineered bacteria into the environment, for agricultural and related purposes, has now led to a second wave of concern. While it is much less intense than the first, the anxieties of a vocal and passionate minority are encouraging excessively restrictive regulations.

In broad perspective, we must recognize that this opposition is part of a growing antiscience movement (Davis 1986), with many additional branches. A major component is environmentalism; and while scientists have every reason to be sympathetic with its main thrust, many of its advocates have unfortunately greatly exaggerated the threats from genetic engineering to the environment. In a closely related movement, the reaction to real problems created by toxic chemicals has led to a phobia about an alleged epidemic of poisoning by traces of chemicals in our environment, even though the death rate and the age-corrected incidence of most cancers (other than those due to smoking) are continuing to decline.

Another manifestation of antiscience is the animal rights movement, a secular equivalent of fundamentalism, appealing to some people troubled by the materialism of our culture and searching for transcendent but nontraditional values. Although this movement is not concerned particularly with engineered bacteria, it will create problems for genetic engineering of animals.

Finally, the antiscience movement is nourished by a broad loss of confidence in the integrity of our social institutions, an attitude that inevitably extends to science, for science is now highly institutionalized. We also see loss of confidence in our ability to deal with rapid change and growing complexity, and there is no doubt that the technological innovations spawned by science are the main reason that social change has become so accelerated in modern times.

All of these branches of the antiscience movement have sprung up in response to real problems generated by science and technology. Unfortunately, we have often been late in recognizing these problems, and the resulting overreaction nostalgically seeks an escape rather than a realistic assessment of costs and benefits. In addition, the unexpected costs and

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risks from the physical technologies have led to the widespread but unwarranted assumption that biotechnology will inevitably have similar effects. Bacteria are especially suspect, for microbes are much more familiar to the public as agents of disease ("germs") than as beneficent partners in the cycle of life on earth, and their invisibility makes them all the more scary. The usual political process of negotiation between opposing forces deals badly with such issues, for they involve not simply opposing interests or values but technical assessments that do not lend themselves to effective popular judgment.

Against this skeptical background we are unlikely to be able to restore an earlier climate, where scientists were trusted to order their own affairs. We face instead an increasing involvement of legislators, regulators, and the public; and if this new alignment is to work well, we need much wider education in biology.

It is particularly important to try to improve public understanding of evolution. For just as the development of nuclear energy gave great practical importance to Einstein's previously esoteric equivalence of mass and energy, so the deep implications of Darwinian evolution for genetic engineering tremendously increase its practical importance. Evolution sheds light on several problems addressed in this paper: the nature of the microbial world, the limits in the power of the new techniques to refashion organisms, and the principles that govern the spread of novel organisms. Perhaps the recognition of these implications, combined with public interest in genetic engineering, will gradually diminish the extraordinarily wide resistance that evolution still faces, at least in the United States.

Meanwhile, lack of appreciation of evolution contributes to anxieties over biotechnology and hence to excessive regulation, which in turn encourages bureaucratization of science. Much more is at stake than merely delays in field testing of new products by industry. Unfortunately, scientists have not responded nearly as broadly as in the 1970s, when all molecular biologists felt their research threatened. Geneticists should be particularly concerned, because this field, with its hubris in delving into the essence of living beings, is so vulnerable to public suspicion.

Roles of empiricism and of theory

The criteria

Let us first look at the problem of regulating biotechnology in general terms: the criteria for regulating any product. When the level of toxicity of a material for humans can be measured, as with radioactive chemicals, benzene, or asbestos, we have a firm base for estimating risks and setting tolerable limits of exposure. Even with the less straightforward problem of preventing enteric infections there is a reasonable scientific base for using the count of the harmless *Escherichia coli* in water for drinking or for swimming as an index of tolerable contamination with sewage. However, with novel recombinant bacteria, derived from nonpathogens, we are asked to prove that there is no danger. How can we prove such a negative?

If damage by the actual organisms released were the source of our concern, as with toxic chemicals, that could be measured. But the issue is really quite different: it is the possibility that the introduced bacteria may proliferate and spread in the environment and that these progeny will then cause harm to some animals or plants outside the area of initial application. (Some ecologists have expressed concern also over the possibility of other kinds of damage to the environment, apart from pathogenesis; but this proposal remains vague and does not specify what to test for.)

Accordingly, if we should have evidence that an organism meets both criteria, being able to spread in some environment and also being pathogenic for some host, then we would have something definite on which to base a standard. But if we test the organism in a range of environments in "microcosms" in the laboratory and all yield negative results for either criterion, this outcome will not exclude the possibility that it could spread in yet another environment or that it might be toxic or infectious to yet another species of potential host organisms. In the end, then, we do not disprove risk: we develop confidence that it is low enough to be ignored.

It is, therefore, an illusion to think that we have based the assessment of risk entirely on empirical tests. These have been extensive for the first few recombinant bacteria designed for introduction to the environment, such as the ice-minus variant of *Pseudomonas syringae*; and the results have demonstrated, as expected, no spread beyond the inoculated plot of land, and no harm to a variety of heavily exposed higher organisms. In the end, however, since we cannot test all possible circumstances, our confidence in the safety of these organisms has relied tacitly on relevant *principles*. These are principles in evolutionary biology, concerned with the factors governing the survival and the distribution of each kind of organism in the environment, and in epidemiology, which is the application of evolutionary biology to pathogenic organisms.

These principles are not synthetic substitutes for hard facts. They have been derived by the integration of a large body of empirical knowledge, in this case, knowledge about differences between pathogens and nonpathogens and about the diversity and the continual genetic variation and gene exchange of the microbes found in nature. These principles are, therefore, a very useful guide in setting up regulations.

I would suggest that even though this aspect of the analysis has not been articulated in our decisions on specific organisms, it has tacitly contributed to our confidence at least as much as our limited series of negative tests on those organisms. If so, I would further suggest that we should make these principles a primary basis for judgment when we start to assess the next organism. Instead of insisting, as a number of ecologists have been doing, that we require extensive tests of every genetic novelty, on a case by case basis, for possible spread and harm, we know enough to justify exempting recombinant products of nonpathogenic bacteria. (Needless to say, any marketed bacteria must be tested, as has been done for those introduced decades ago, for possible toxicity to persons who will be handling the material.)

Risk assessment and resilience

The problem that we are discussing is a specific example of the general problem of risk assessment and decision making, which has generated an extensive literature in the social sciences. I cannot pretend to be very familiar with this literature, but I have been impressed with a thesis expressed by Douglas and Wildavsky (1983) in their book *Risk and Culture*. As they point out, administrative law, in many areas, has responded to unrealistic public expectations by pretending that we can foresee and prevent harm more effectively than we actually can. As a result we create clumsy, wasteful bureaucracies, which impede progress without providing real protec-

tion. These authors suggest an alternative that they call resilience: a policy of watching new developments more closely and responding to them more rapidly, rather than trying to guess them ahead of time.

This approach should appeal to scientists, for it is close to our traditions: a pragmatic approach, recognizing that the Darwinian principle of trial and error is pervasive, and that the outcome of many actions can be described only in stochastic terms. These traditions contrast with the more formal and rigid traditions of the law, based on the assumption of a deterministic world, and emphasizing the value of detailed, established procedures rather than a resilient approach to the search for the correct answer.

Are serious consequences without warning possible?

We return to bacteria. The advocates of great caution emphasize that even if there is only a very small probability that some novel strain might spread and cause harm, we are obligated to take the possibility seriously, because the harm might be so great. However, this position creates a dilemma. Because of the nature of the microbial world, if such spread should occur, we could not expect to be able to reverse or contain it. Hence, if we believed the possibility of harmful spread of a particular organism is a realistic concern, logic dictates that we should never permit it to be tested in the field!

In fact, although some countries, taking seriously the rhetoric of the search for absolute security, have established a 5-year moratorium on field testing of any genetically engineered bacteria, many countries do allow field testing, on the basis of probabilities, and the organisms that they release do not recognize national boundaries. We have thus lost our virginity, so to speak, by accepting the criterion of a reasonably low probability. However, we already have evidence that nonpathogens meet this criterion. Accordingly, the concept of resilience should lead us to exempt this large class of organisms from the requirement of extensive pretesting.

Let us now move from these philosophical considerations to specific features of engineered organisms.

The Recombinant DNA Advisory Committee guidelines

Because the problem of the introduction of engineered bacteria to the environment is very similar to the earlier problem of accidental release from the research laboratory, it may be useful to review briefly the reasons that the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) relaxed its initially stringent guidelines for this research.

The RAC was established on the basis of the widespread assumption, initiated by molecular biologists, that recombinant bacteria must be assumed to be dangerous until proved otherwise. The guidelines were initially severe, requiring the use of mutant strains of *E. coli* that could not grow outside the laboratory (biological containment) and restricting large classes of experiments to high-security facilities (physical containment).

Over the next half-dozen years the restrictions were gradually relaxed, for several reasons. Specific experiments confirmed the expectation that enfeebled recombinant strains could not survive and spread. However, the main reason was no doubt simply experience, which allays nervousness. Research with recombinants expanded into hundreds of laboratories all over the world, and with a variety of nonpathogenic organisms, and no detectable harm ensued. It became increasingly evident that the initial, elaborate classification, requiring many different degrees of biosafety for different kinds of recombinants, was highly artificial; it had simply been a device to create confidence (among the scientists as well as the public) that the dangers were being handled responsibly.

Finally, public attention inevitably waned with time. Most molecular biologists were probably convinced within a few months that their initial apprehensions had led to excessive restrictions, but it took a few years before the NIH felt that substantial relaxation was politically and psychologically feasible. Today only experiments with a pathogenic component require federal approval.

Early in the debate a few scientists called attention to evolutionary principles that offered strong reassurance against the hypothetical dangers. One argument was that the introduction of DNA from distant sources into bacteria is not so novel after all, because the steps in this methodology were simply improvements in the efficiency of processes already occurring in nature; hence it is virtually certain that bacteria in nature have always been taking up foreign DNA from distant sources, at a very low rate. A second principle is that evolution selects for balanced, harmonious genomes, and so any alteration that humans introduce into an organism found in nature is almost certain to decrease rather than to increase its competitiveness in the natural world.

The first of these principles was supported by experiments demonstrating that the enzymes responsible for splicing DNA in vitro could also carry out the same reaction, at the same DNA sites, in the bacterial cell. I suspect that the second principle was also recognized, tacitly, by scientists participating in the decisions made by the RAC, but it no doubt seemed too theoretical to present as a justification. This omission may have been unfortunate, since it is a fundamental principle that applies equally to the current problem of deliberate introduction, and its articulation in the course of the successful relaxation might have attenuated the second wave of concern.

The main implication of the relaxation of the guidelines by the RAC can be stated as follows: assessment of the potential danger of an organism should focus on its nature and not on its provenance by a particular technique. Although the RAC is still set up by law to deal only with recombinant DNA, the focus on this technique as a special basis for regulation has become obsolete. Pathogenicity is the decisive feature.

Concern over deliberate introduction

As I have already noted, current public concern over deliberate introduction of engineered bacteria is clearly much less intense than the earlier concern over accidental escape. Nevertheless, it could have a more obstructive effect in the long run, for instead of dealing with the readily modified guidelines of the RAC for research, we are now dealing with the regulation of materials intended for commercial distribution. The several agencies that share this responsibility do not have the broad base of the NIH in the biomedical community, and they are more responsive to political pressures based on perceptions of danger. Thus the NIH RAC approved testing of the ice-minus bacteria noted above, but the Environmental Protection Agency (EPA) and the courts then held it up for several years, despite its obvious safety.

In the current debate over the regulation of engineered bacteria, Adelberg (1988) has classified the participants into three main groups. The reactionaries, such as Jeremy Rifkin in the United States and the Greens in Europe, are opposed to all

genetic engineering, although when they oppose specific activities, they often do not openly reveal their broader agenda. The conservatives, including many environmentalists and ecologists, do not object in principle to genetic engineering and even welcome its potentiality for replacing toxic chemicals in agriculture, but they desire that all engineered organisms be dealt with on a case by case basis, and they press for extensive testing before field testing. They also wish to see field testing expanded only very slowly, while accumulating experience dissolves their anxiety, as in the first wave.

The moderates, including most microbiologists and molecular biologists, would exempt large classes of nonpathogens but would proceed very cautiously where there is some positive basis for suspecting possible harm, that is, in work with pathogenic bacteria, or with bacterial genes related to pathogenicity, and in all work with viruses. Some might consider this view extreme or radical, but logical symmetry would define as true radicals those who are opposed to any restrictions, and I do not know of any members of such a group.

The underlying assumptions

Since our experience with accidental release is clearly relevant to the problem of deliberate introduction, the basic question is whether the differences justify the belief that the latter presents substantial new dangers. We must therefore scrutinize the assumptions that underlie this belief. The following seem crucial. (*i*) An increased scale of the release increases the possibility of harm. (*ii*) The greater the evolutionary distance between the source of the DNA and the recipient in a recombination, the more unpredictable are the properties of the product, and hence the greater the danger. (*iii*) Just as some organisms transplanted from a distant land ("exotics") have multiplied excessively and become pests, so novel engineered organisms are likely to have similar effects. (*iv*) Although the probability of harm is small, the harm might be great and so we must be very careful. (*v*) Our powers to refashion organisms by the new techniques of genetic manipulation are virtually unlimited; hence we need to be very careful about the precedents that we are setting, and not simply responsive to the specifics of the present cases.

Elsewhere I have discussed these and other aspects of the problem at greater length (Davis 1987). Here I shall review the key arguments briefly, emphasizing that they all involve evolutionary considerations.

Implications of evolution

Scale

The presumption that scale is important arises by extrapolation from the effects of toxic or of radioactive chemicals. The scale of a release clearly is crucial for damage from these agents, and the EPA sensibly allows testing of potentially toxic agricultural chemicals to be extended from the greenhouse only to a 10-acre (1 acre = 0.405 ha) plot before allowing wider use. However, with an engineered bacterium there is no logical basis for the notion that a 10-acre plot will limit the danger. As I noted above, what is feared is not damage by the deposited organisms but the uncontrollable multiplication and spread of their progeny. And the dominant factor here is not inoculum size but competitiveness.

Spread can be initiated by a few organisms carried out of a laboratory or a greenhouse on shoes, just as an epidemic of human infection can spread from a single index case. And just as an epidemic depends on a receptive environment (i.e., a high enough density of susceptible hosts), so spread in the soil or on vegetation depends primarily on whether the new organism can outgrow those that are already there. However, the soil is essentially saturated, with a very dense and enormously varied population (averaging around 10^6 bacteria per gram), utilizing each food source as it appears.

Accordingly, we can alter the distribution of the soil flora most readily not by introducing a novel organism but by altering the environment. A dramatic example is the rapid increase of bacteria resistant to a particular antibiotic, in the human and the animal population, as a result of selection by the widespread use of the antibiotic. Similarly, the eutrophication of a lake is not due to the introduction of anaerobes but is due to an increased level of nutrients, creating a greater oxygen demand than can be met and hence allowing outgrowth of anaerobes.

The concept of scale raises another evolutionary consideration. Our laboratory experiments are puny compared with the enormous scale of the evolutionary variation and selection that is constantly going on in the soil flora, based as noted above, on gene transfer as well as on mutation. Hence whatever novel organism we introduce, it seems exceedingly unlikely that a similar organism will not already have appeared in the long history of evolution, and hence have been selected for or against. Whatever is alive today is descended from organisms that have survived exposure to this continual supply of variant bacteria.

Evolutionary distance

This concept has played a major role in regulation thus far. The current regulations of the EPA in the United States exempt recombinants between nonpathogens when they belong to the same genus (although there is considerable pressure to remove this exemption). Recombinations between different genera are not exempted, on the grounds that they are much less likely to occur in nature, and so their products are less predictable.

In fact, however, evolutionary considerations would lead to the opposite conclusion. If we take it as a sound general principle that well-adapted organisms must have a harmonious, balanced genome, whose various genes and gene products interact effectively, it follows that DNA from a more distant source is less likely to fit well into its host's genome than DNA from a closely related source. Although science fiction may scare people with pictures of misshapen monsters, evolutionary success, i.e., effective competition with the organisms that are already present, depends on a shapely fit of the parts.

This kind of evolutionary reasoning also applies specifically to pathogens. The adaptation of a pathogen to its host, and its ability to be transmitted efficiently, requires a set of appropriate genes, involving a number of mechanisms (which are being rapidly untangled in the relatively new field of molecular pathogenesis). One does not make an effective pathogen, able to compete and spread, by simply inserting a gene for a powerful toxin.

In the famous ice-minus case the shift was in the opposite direction: the recombinant was deprived of its original pathogenic action by removing the gene for an essential component in that process, a surface protein that could nucleate ice formation. In effect, the organism was an analogue, for plants, of an attenuated live vaccine for animals and humans. Moreover, while such vaccines have had to face the problem of possible genetic reversion to the pathogenic form, there is even less reason for concern about the ice-minus strain. Not only would

its genetic deletion prevent reversion, but the "pathogen" to which it might have reverted is not an occasional agent of infection: it is a regular inhabitant of the leaf surfaces. The eventual testing of this recombinant required years of legal struggle and great expense, illustrating the difficulty in getting the scientific realities in this area to previal over bureaucratic procedures and emotional perceptions.

Two models: transplantation versus domestication

Ecologists have necessarily been deeply concerned about the disastrous ecological effects of various transplants between continents, such as gypsy moths and starlings. This model loomed large in the initial objections from a number of members of this profession to the introduction of engineered organisms. By now, however, this argument appears to have been largely abandoned, with the recognition of major differences between shifting the nature of an organism and shifting its environment. Transplants are naturally occurring organisms that have been well adapted to the wild by a long period of evolution; when they are moved to a new locality their multiplication may explode for lack of the predators and parasites that have previously limited their populations. In contrast, with engineered organisms, the genetic manipulations will almost certainly not improve their adaptation to their original environment (and will ordinarily decrease it), and it is that environment to which they are returned.

A much closer model is provided by domestication, a form of biotechnology that mankind has been practicing for thousands of years, on animals, plants, and microbes. In this process people select for naturally occurring variants with altered traits that are of value for us, rather than of value for survival in the wild. Genetic engineering is a technique for accelerating domestication and broadening its range. In addition, in contrast to the modern physical technologies, domestication has given us enormous benefits without accompanying adventitious costs. There is no obvious reason to expect that domestication based on improved techniques of variation will produce such costs.

To be sure, past domestication, especially of plants and animals rather than microbes, has been responsible for developments that can be seen in a broad perspective as costs: displacement of the wild by cultivated areas, and explosive increase of the human population. However, these have been consequences of our intentional use of these organisms, rather than adventitious products of their autonomous activities, and in principle we should be able to control these uses. In practice, however, it is difficult, because the uses are based on economic and health benefits and the pressure to welcome anything that increases survival, multiplication, and power has deep evolutionary roots.

The implications for genetic engineering are clear: the real danger is not that the novel organisms will spread beyond our control but that they will be cultivated on an excessive scale and hence will accelerate the undesirable indirect effects of domestication. If we are to prevent this consequence, the regulations that would be required are quite different from those that would aim at prevention of adventitious spread.

Low probability but high risk

The conservatives and the moderates in this controversy seem to agree that the chance of harm from recombination among nonpathogenic bacteria is very small. However, the conservatives feel that even a small chance requires great care, because the harm might be great and the spreading novel organisms could not be recalled. If most microbiologists, in contrast, are less worried, it is not only because of the features of the microbial world described above; it is also because pathogenicity has the additional feature of varying quantitatively in its level, i.e., it can be shifted up or down by various mutations, in a number of different genes. Hence, if a nonpathogen were to move toward becoming pathogenic through a series of genetic changes, whether introduced by molecular recombination or by other techniques, there is every reason to believe that the degree of pathogenicity would build up gradually, as in any evolutionary process of perfecting a new trait by successive refinements.

In consequence, built into any realistic scenario for adventitious harmful spread of a recombinant is an early warning system before serious problems would arise. Since the enormous experience with nonpathogenic recombinants in the laboratory has not given us any trace of a warning, it seems reasonable to conclude that the chance of serious harm is not only small: it is negligible.

Good judgment would seem to require further that in assessing the danger from introductions on a large scale we should cease invoking a related pseudomathematical formulation of the danger as the product of nearly zero times nearly infinity. The initial wave of concern over recombinants had to deal with this argument, based on an unrealistic demand for absolute security, rather than settling for a realistic probability, as we do in all other aspects of our lives. We should not have to go through this process all over again, as though our extensive experience with recombinants were irrelevant.

Power to reshape the living world

Since we can now vary DNA sequences at will, without limits, the public has been given the impression that we will also be able to refashion organisms at will, without limits, and so we may be opening Pandora's box. However, evolution sets much narrower limits to our powers. The creation of a successful organism depends not only on variation but equally on natural selection; and while the new techniques radically change the possibilities for variation, they do not influence natural selection. In that process an organism has evolved its genome through a long path, constantly selecting for balance; and this requirement severely restricts the range of the next steps that are consistent with viability, let alone with competitiveness in the wild. We will not be creating square cows or angels with four limbs plus wings.

One caveat is necessary: the factors that limit possible variation in a higher organism include not only functional interactions between the parts in the developed organism but also the little understood process of development. Some day, when we understand this process better, we may be able to produce more radical chimeras than seem imaginable today. However, this possibility is too far off to be relevant to current problems of regulation.

Conclusions

The arguments presented in this paper, based largely on evolutionary principles, lead to the conclusion that deliberate introduction of engineered bacteria into the environment does not present a significantly greater hazard than their accidental escape from the laboratory or the greenhouse, an earlier concern that has now subsided. Moreover, these organisms should not be regarded with any greater suspicion than the several dozen kinds of bacteria, including products of classical genetic

engineering, that have been on the market for many years for use in agriculture and in mining. Lack of appreciation of the relevant evolutionary principles has led to overregulation of the use of engineered bacteria in the environment, in the United States and even more in some other countries.

Since it seems unlikely that regulatory agencies will rapidly exempt all recombinants derived from nonpathogens, one could argue that the position presented here is too far from the center to be politically effective. However, I have proceeded on the assumption that when a scientist is trying to analyze scientific issues with social implications, his obligation is not to temper his conclusions to make them politically more acceptable, but is rather to present them in unvarnished form. Other groups, taking this information into account, will then have to balance it with other considerations in making policy.

As our society struggles with novel problems presented by genetically engineered bacteria, we can best help it to develop a resilient approach by emphasizing applicable scientific principles among which implications of evolutionary biology loom large.

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Limits to genetic intervention in humans: somatic and germline

Bernard D. Davis

Bacterial Physiology Unit, Harvard Medical School, Boston, MA 02115, USA

Abstract. The promise of somatic cell gene therapy is likely to be limited to a narrow range of monogenic hereditary defects. This therapy raises few moral issues. However, extension to the 'improvement' of a normal trait might raise problems, similar to the use of hormones in sports. Another danger is uses that result, like heroic measures to save the premature newborn, in the prolongation of misery and in intolerable expense.

The genetic alteration of germline cells, which can already be accomplished in animals, is in principle applicable to all monogenic diseases. Its use in humans is much less acceptable than somatic cell therapy. The objection that it tampers with human evolution is widely cited. However, more important may be the risk of producing a new defect, for risk is much less acceptable in a yet unborn person than in an already ill individual. In addition, the goal of germline therapy could almost always be accomplished more simply and safely by prenatal diagnosis and selective abortion.

The highly polygenic nature of the most interesting traits, both behavioural and physical, makes it unlikely that we shall be able to modify them usefully in the foreseeable future by either somatic or germline intervention. Despite this delivery from temptation, public fear of future 'blueprinting' of humans no doubt contributes to a multi-faceted antiscience movement.

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The possibilities for altering genes in humans fall into two classes. Somatic gene therapy aims at correcting the defect in specific cells in patients already born with a hereditary disease, while intervention in a germline cell results in transmission of the desired gene to all the cells of the developing embryo and hence also to subsequent generations. Since the term 'genetic engineering' has an inappropriate implication of technocratic rather than medical values it seems preferable to designate germline intervention also as a form of gene therapy, though it is, strictly speaking, prevention rather than treatment.

A few years ago, with the prospects for such therapy apparently drawing near, a Presidential Commission in the United States analysed the issues very well.

Their report, entitled 'Splicing Life' (1982), emphasized the need to distinguish the very different moral issues raised by the two different approaches.

Somatic gene therapy

The Commission could find no obstacles to proceeding enthusiastically with somatic gene therapy. The incorporation of a gene to treat a disease in an individual seems morally no different from the repeated administration of the product of that gene, and even if it entails some risk it would be justified by the illness of the recipient.

This point of view now seems to be widely accepted. Unlike the introduction of genetically engineered bacteria into the environment, where extreme opponents such as the Green parties in Europe have a considerable following among environmentalists and have received support from many ecologists, similar opposition to gene therapy has not appealed to the public. The opposition of a group of theologians in the United States a few years ago, initiated by Jeremy Rifkin, has died down and even resulted in some apologies, and significant future opposition seems unlikely as long as the procedure is used only for the treatment of illness.

The main limitation of somatic gene therapy is that it can be expected to be beneficial in only a very limited range of hereditary diseases. In principle, infecting a patient with a retrovirus carrying a desired gene might be able to introduce it into cells throughout the body, but the prospect of doing so effectively and safely seems remote. A more promising alternative is to incorporate the gene into cells taken from the patient, select the altered cells, culture them in quantity, and then colonize them in an appropriate tissue in the body—possibly after depleting that tissue of the defective cells to be displaced.

The most favourable candidate for such therapy is the haemopoietic system in the bone marrow, because its diffuse structure permits cells to perform equivalent functions without very specific localization, whereas most cells in other organs would have to be replaced in their proper location in a highly organized tissue. Moreover, cells not only leave the marrow for the bloodstream but also can enter it, in the reverse direction. Initially it was thought that the best candidates for gene therapy would be the numerous hereditary defects in red blood cells, such as thalassaemia and sickle-cell anaemia. Now, however, it seems that defects of the immune system are more immediately promising, for technical reasons. Among these, an improvement in function may not require as extensive replacement of defective by effective cells.

After a wave of optimism a few years ago, the technical obstacles to gene therapy proved to be more formidable than was anticipated, and, in fact, greater than those encountered in germline alteration. One limitation is that most of the cells recovered from the marrow are too mature to initiate colonization,

and the required stem cells are less than 1% of the total. Another is the poor expression of genes transferred in this way. However, means for enriching preparations with the desired cells, and for increasing the output of the desired product, are being sought.

Very recently the first approved experiment for administering genetically altered cells was carried out, at the National Institutes of Health in Bethesda, Maryland. It is, in fact, not strictly an experiment in therapy but is a test in which an easily detected genetic marker has been incorporated into lymphoid cells, which are then injected in cancer patients with very limited life expectancy. There is good reason to expect that the outcome will reveal no obstacle to trying similar treatment with genetically modified marrow stem cells.

How far the technique can be extended beyond the bone marrow is not clear. Cells that secrete hormones are candidates, since they can presumably function without a specific location. In the liver the relative uniformity and simple arrangement of the hepatocytes may conceivably permit their replacement. In contrast, cystic fibrosis, the most frequent monogenic hereditary defect in Caucasians, is a very unpromising candidate, because the defective gene causes altered membrane function in a variety of organs, ranging from the lungs to the sweat glands.

Perhaps the greatest extension, trying to look beyond the immediate future, will lie not in curing monogenic hereditary defects but in reinforcing various functions to help to combat other diseases. In particular, our rapidly advancing recognition of the role of immune responses in a wide variety of chronic and degenerative diseases, as well as in infections, suggests the possibility of instilling genetically altered cells to modify those responses—for example, to stimulate interferon production, to increase the effectiveness of the immune response to specific antigens, or to inhibit autoimmune responses. This development would require not only further advances in the field of immunology but also solutions to the problem of achieving good expression of the desired genes.

Understandably, the possibility of another future use of somatic gene modification, not only to treat disease but also to 'improve' people, has generated concern. For example, a gene for growth hormone might be used to increase height, and perhaps other hormonal alterations to increase strength. But, even if we find such uses trivial or repugnant, a world that accepts cosmetic surgery and the injection of silicone to enlarge breasts, and that cannot prevent the use of hormones by athletes, may find it difficult to limit non-medical uses of somatic genetic alteration if there is a market. We, or our successors, will have to deal with the problems in this area as they arise. Fortunately, the foreseeable range of technical possibility is extremely limited: the most tempting traits, such as beauty or various mental traits, are too polygenic to seem feasible as candidates.

I would like to suggest a different possible misuse, which has not drawn attention. Along with the triumphs of modern advances in medicine a tragic

side-product has been the use of heroic measures to keep alive bodies that are only a source of prolonged misery for the individuals and their families, and often at an expense that society is finding it increasingly difficult to support. These problems arise at both ends of life: premature or grossly defective births, and the terminally ill. If some of the applications of gene therapy should provide only prolongation of life without restoration of reasonable quality, one would hope that such cases will not automatically become subjects for this most extreme of heroic therapies.

Germline therapy

Unlike genetic alteration in somatic cells, alteration in fertilized eggs of mammals, or in the functionally equivalent cells from early embryos, is already possible. The resulting transgenic animals are widely used for experimental purposes and may soon be used in agriculture, and in principle the technique could also be used on humans. However, so far it has serious limitations. Only a few per cent of the treated germ cells incorporate the foreign DNA into the genome. Moreover, instead of replacing the defective gene the new gene is added; and since it enters at random sites on a chromosome it occasionally results in a grave defect by interrupting the sequence of another gene. However, techniques for the homologous recombination of the foreign DNA with the defective gene, which should result in replacement rather than in addition, are being sought.

Because this form of gene therapy reaches all the cells of an organism it could be applied, unlike somatic therapy, to any monogenic disease, including those that affect multiple tissues. Moreover, preventing an abnormality in this way is clearly preferable to seeking a cure after the birth of an impaired individual.

The procedure has also been thought to provide an additional advantage for the individual as a future parent, and also for society and for human evolution, by preventing the transmission of the defect to future generations. But this advantage seems at present illusory. The techniques now in sight add the corrective gene rather than replace the defective one, and so the latter is still perpetuated; and in such individuals some of the germ cells in the next generation would be expected to segregate the defective gene from the correction, thus allowing the defect to reappear.

In addition—to discuss a highly theoretical issue—the main problem in preventive genetics is the homozygotes formed by the mating of two heterozygotes. Accordingly, if germline therapy is eventually to be used in humans it would probably have to await the ability to identify cells from early embryos as homozygous for a defect, since one would be unlikely to wish to use an elaborate technique on cells that were not homozygous. Moreover, if we consider not only the cure of the individual but also the evolutionary ideal of eliminating defective genes, it would obviously be even more difficult to replace both defective genes in a homozygote than to replace one in a heterozygote.

The Presidential Commission strongly opposed the application of germline intervention in humans. Their main argument was that altering human genes in a heritable way would be taking human evolution into our hands—a Promethean undertaking that we should not initiate. I do not find this evolutionary argument very convincing. For one thing, the consequences for subsequent generations are not clear: as I have just noted, the introduced gene will not ordinarily displace the defective one. But, even if that limitation proves not to be permanent, the precedent of influencing human evolution is not so novel. We already do so by any actions that differentially affect the relative quantitative contributions of different parts of the population to the gene pool of the next generation. For example, genetic counselling may lead carriers of defective genes to avoid having children, while prenatal diagnosis may allow them to dare to have children. More broadly, as the distinguished geneticist J. B. S. Haldane noted many decades ago, any change in the tax structure slightly affects the gene pool by influencing decisions about family size.

What the Commission and others really feared, of course, is that use of the technique of germline intervention for medical purposes would open the door to its use to 'improve' people, and here the range might be much broader than with somatic cell therapy. The original concern was over a 'Brave New World' imposed by governmental authority, but bioethicists soon realized that a more likely social problem would be consumers purchasing desired genes on the free market. But here we have a safeguard: the traits of greatest interest for any eugenic programme are highly polygenic, and that complexity would make them poor candidates for significant, predictable modification by genetic intervention.

Let me also note a historical safeguard. The classical methods of selective breeding of domesticated animals, which have proved to be so spectacularly effective for thousands of years, could have been used equally in human populations if there were agreement on the desired phenotypes to select for. But mankind has shown little interest in such programmes of positive eugenics (except for the genetically misguided ancient experiment of India with castes: see Dobzhansky 1962). To be sure, the new techniques might be more tempting, since they should offer more precisely predictable changes than the statistical probabilities of a breeding programme. But fortunately, the most tempting traits seem likely to continue to be very resistant to precise eugenic intervention, and this limitation will give us a good deal of time to adapt to the new techniques and to decide what non-medical uses to allow, if any. Gene therapy need not follow the precedent of the technological imperative, in which whatever can be done usually will be done if it seems likely to produce benefits or profits.

Meanwhile, I share, though for other reasons, the conclusion of the Commission that we should not undertake germline intervention in the foreseeable future. One reason is that the technique would have to become extraordinarily safe before responsible physicians would be interested. For while some degree of risk in the treatment of an already seriously ill person is

traditionally acceptable, it is another matter to take responsibility for a statistical probability of producing life-long damage to a person yet unborn. It is therefore hard to imagine that any responsible medical investigator will be tempted in the near future to undertake such experiments in humans, even though the techniques are already at hand.

The second objection to germline intervention is that prenatal diagnosis, leading to selective abortion, already provides in most cases a much simpler and safer way to reach the same goal: to prevent the production of a homozygous, defective infant by a pair of parents who both carry the same recessive defect. And, despite the present intense objection of much of the population to abortion, these objections will surely have to adapt to our rapidly growing ability to predict and prevent genetic catastrophes that formerly had to be viewed fatalistically as 'acts of God'.

Conclusions

The highly polygenic nature of the most interesting traits, both behavioural and physical, makes it unlikely that we will be able to modify them significantly in the foreseeable future by either somatic or germline intervention. Despite this delivery from temptation, public fear of future 'blueprinting' of humans no doubt contributes to a growing multifaceted antiscience movement (Shils 1986). Adherents of this movement take the benefits of science and technology for granted and then focus on exaggerations of real or hypothetical accompanying risks and problems, whether in relation to nuclear energy, toxic chemicals, animal rights, or the social implications of human genetic diversity. The additional prospect of intervention in man's inner nature—his genes—may strike at the deepest roots of all. To promote a healthy relationship between scientists and the rest of society it is important for scientists to try to educate the public on the limits, as well as the dazzling promise, of our new power to manipulate genes.

It is also important to recognize that even if some of the worrisome prospects that I have discarded as unlikely turn out to be true in the long-enough run, it is only for a relatively short run that we are able to set up guidelines or regulations intelligently. In a world in which science and technology are changing our patterns of living and our problems with unprecedented speed, resilience in response (Douglas & Wildavsky 1982) is likely to be more effective than efforts at detailed anticipation.

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DISCUSSION

Nossal: I profoundly agree with the thrust of your analysis. It is so vital to get the point about the polygenic nature of the most important human traits across to the public. Your emphasis on the unreality of gene therapy being used in a eugenic sense is enormously timely and very important as a counterbalance to some of the exaggerated views of the dangers of human genetic intervention held by single-issue pressure groups. It is important to get this debate back on the rails.

Williams: This is a relevant point but I think it needs to be taken one stage further. Besides insisting on the point that most of the characteristics that people would be interested in from a positive eugenic point of view are highly polygenic and therefore present these difficulties, you have also to do something to improve people's understanding of moral argument. It is natural to say that what people need to grasp is the *principle* of the matter, and that they won't have done this unless they know what to say about a highly desirable character that does not present the technical problems of polygenic characteristics. You cannot simply leave the question at the level of saying that modifying polygenic traits by genetic means is technically highly improbable; you have to take it a stage further. The sensitive issue is *how* much further. It is a requirement on moral argument that it shouldn't simply stop at a mere technical fact, and say that the question doesn't arise; but it is *not* a requirement on a moral argument (in my view) that it should be able to cope with any conceivable possibility.

Now, the grades of possibility that a moral argument has to deal with, and how remote they can be (and this ties up with the Chairman's introductory comments on the three grades of probability of things being done), are matters of disagreement between various views of moral reasoning. The only point I want to make is that you won't achieve the results you want about the moral discussion of these eugenic issues simply by insisting on practical impossibilities.

Davis: An ancient principle in ethics is that 'ought' implies 'can'. If so, moral arguments about things that are impossible become just exercises or games. So, if we could prove that geneticists can effectively modify only monogenic defects, we would have no moral obligation to argue about the polygenic characteristics that people are in fact concerned about. But if we are still left with non-medical modifications of monogenic traits—say, the example of growth hormone and height—I would be happy to concede the point that in order to avoid fears of more extensive blueprinting of people (even if the fears aren't realistic) we should keep the 'gate' of even such a harmless intervention as increased height closed, at least for the near future.

Williams: Not all moral argument is about 'ought', however. Much moral argument is about 'good', and 'good' doesn't imply 'can'. In any case, we are concerned not with 'obligations' but with 'permissions', and one of the ways we think about what is permitted is to consider what we would regard as

permitted if some particular kind of action were possible. Thus my point is that we have to go beyond the narrow bounds set by 'ought' and 'can' into the area of 'might be permissible, if it were possible'.

Davis: But should we be concerned about 'ought not' (i.e., is not permitted) where we cannot?

Dixon: I want to support Professor Williams, because scientists tend to argue similarly that certain possibilities are too complicated to attain, or are 'unthinkable'. But in the public debate this easily gives the moral ground to the opponents of particular developments, because their position on many such issues is very clear: they should not be done. Their very explicit view appeals to many people in the general public. In the midst of this the scientific community is often lacking any thought-out philosophical or even ethical viewpoint. Simply saying that something is unthinkable or too technically difficult to contemplate is a cop-out.

Weissmann: I would like to mention a genetic germline intervention, namely 'genetic immunization', which might become feasible in the not too distant future. The idea is to introduce into the germline a gene that will prevent infection by a specific virus, for example by giving rise to a protein which would act as a repressor of an essential viral gene, or bind and inactivate a virus-specific transcription factor. In particular, AIDS virus (human immunodeficiency virus, HIV) might be a possible candidate for this, because it expresses several regulatory proteins which are most likely virus specific, such a *tat*, *nef* and *rev*. I would imagine that such a genetic procedure might become possible in the next few years. It would be the counterpart of a monogenic intervention, and it would have a medical purpose.

Brahams: How far should you take into account that if you interfere now, with germline immunization, techniques may improve and alter in the future, even in 10 years, say, but the descendants of those immunized by this means would still be affected by what you have done now? I am playing Devil's Advocate here, but you would be committing yourself for future generations on present-day science. Science moves so quickly that 10 years is a long time; 30 years is a very long time.

Brenner: Charles Weissmann's suggestion of genetic immunization against virus infection might also be achieved by somatic cells; you would not have to change the germ line. I have even heard it argued that this should be done by using skin, so that if something untoward happens it can be easily removed.

Nossal: This is like the proposed artificial pancreas, which would depend on persuading a removable skin graft to secrete insulin. But the technology for that is so far in the future that it is like science fiction.

Williamson: A group is now transplanting isogenic (genetically identical) liver tissue as a patch under the skin, in order to treat hypercholesterolaemia, in a rabbit model, and it appears to work; so gene therapy by tissue transplantation is not science fiction at all.

I actually don't see such a clear distinction between polygenic, multifactorial conditions and single-gene defects. Hypercholesterolaemia is the most obvious instance where one might remedy a defect which is definitely multifactorial in causation by making an alteration in a single gene, such as that for apolipoprotein B. This is a very clear model because we know some of the genes that are involved. There is every reason to think that we will know some of the genes involved in more controversial areas, such as depressive illness, in time. I would like to accept your model, Dr Davis, but my experience with hypercholesterolaemia in relation to coronary heart disease and diabetes makes me reluctant to do so. I think we shall find that the problems of polygenic disease will be more complex, because it may be that there are 10 genes, and the environment, involved; nonetheless you can have an impact on the phenotype by altering just one of those genes.

Motulsky: In a similar way, if we take 'intelligence' as an example, it is conceivable that very many genes are involved but there may well be one major gene that contributes 30% of the variance between individuals. If you could manipulate that gene, there might be a demand to improve intelligence in this manner. So, even with a polygenic trait where many genes are involved, certain genes may have much more of an impact on the final phenotype.

Pembrey: Dr Davis, and Dr Bell, have referred to the alternative of prenatal diagnosis followed by selective abortion. But if one takes it further, as Anne McLaren mentioned (p 27), and considers preimplantation diagnosis and the selection of embryos, prior to implantation, that makes most of the debates about germline therapy for the correction of monogenic disorders redundant. For germline therapy, you must be able to diagnose an embryo as being affected by a genetic disease before you can alter it and, if you can do that, then you can select another embryo out of the dish that has a winning combination of genes, and implant that instead. Rather than talk about what scientists might want or not want to do, a more valid question is to ask what parents would want. In such situations they would have a stark choice, between being the first person to have this germline gene therapy and it might work, but there may be risks; or having an embryo with a winning combination of the couple's genes. Which embryo would they want put back? Those of us who deal with the clinical situation know what the answer would be—embryo selection.

Brahams: On this general point of eugenics and the fear of germline manipulation, we have after all been fiddling with the fitness of the human species for a long time; people have used various quite crude methods through the ages to obtain what they want. The Spartans left newborn babies out at night so that only the fittest would live on to add to the race; those that failed to survive were not wanted anyway because it was thought they would weaken the race. Today, some cultures don't like to have too many girls, so they may get rid of female babies, or at least some of them, at birth. We can now sex babies before birth: abortions take place on the basis of sex. We also, as

Dr Davis said, accept cosmetic surgery, or straightening of teeth, and therefore people who might not have found partners because of their unattractive appearance are now reproducing. We are effectively changing our racial gene structure already by obstetric manipulation. Is germline genetic alteration so fundamentally different? It is another way of manipulating the human organism, but from inside rather than from outside, 'in the hopes of improvement'.

Nossal: Is there not still a fundamental point that the straightened nose is a somatic intervention with no implications for the race downstream, whereas the genetically engineered straightened nose is passed on down the generations?

Brenner: What about knowledge-based mate selection? In other words, suppose we don't leave the genetics to naive interpretation of phenotype but we inject scientific knowledge. We could have a dating bureau where you could not only say that someone has certain looks, but actually has genes for those looks. Photographs of people would come with Southern blots. We could even have kits for fingerprinting girlfriends; only one hair would have to be plucked, after all.

Debenham: There are *already* sperm banks of Nobel Prize winners, and women can write in and obtain sperm from individuals noted for characteristics of athletic ability, intelligence, musical abilities, good looks, and so on; children are being born from the chosen sperm. I just wonder whether those sperm are now being characterized for their cystic fibrosis carrier status and conditions like that?

Brahams: That brings us back to Bernard Shaw's aphorism and the fact that some unwanted traits might emerge as dominant and you may not get the effect you hoped for.

Debenham: Nonetheless, pre-selection is going on, on the basis of characteristics for which we don't know the genetics; but I wonder whether we are adding in, now, the information that that sperm donor carries genes for, say, a monogenic disorder.

McLaren: One has to remember that for many millennia there has been selection for mates on the basis of phenotype, and it's well established that there is assortative mating for all sorts of characteristics that have been looked at; in other words, people tend to choose mates who are rather like themselves. And phenotype is not a bad indication of genotype.

Zimmerli: That an action is acceptable because it has already been performed by others obviously isn't a valid moral argument either: it could have been wrong all the time!

But I wanted to come back to Professor Williams' earlier question concerning what might be permissible if it were possible. One of the 'might be permissible if possible' principles he was looking for could be the *principle of inter-generational fairness*. In applying this principle you would have to decide (or rather assess) whether it might be fair to future generations to withhold or to deliver the genetic information in question, if it were possible to do so, as in the case you mentioned, Dr Weissmann. My moral judgement in that instance

is—as you are well aware—quite different from yours, because I think that there exists something like a *categoric borderline* dividing the permissible from the prohibited and that from this very borderline it follows that human beings *must* under *no* conditions whatever tamper with human germlines! This is of course not an argument, but an assertion about my convictions with regard to the existence of categoric borderlines in ethics. If, however, you look at it as if it were a possible moral argument, then you would have to deal with it as a consequentialist argument and you would therefore have to ask: what are the possible benefits—i.e., which of the consequences will be considered *good* by future generations—and what are the possible negative side-effects and risks—i.e., which of the consequences will be considered *bad* by them (and maybe by us too)?

Weissmann: I was actually trying to reduce it to a situation where you *can* make the judgement: is it legitimate to interfere with the germline if you have a very high ratio of gain to risk? That is an example which could be discussed in relation to this moral issue.

Zimmerli: This shows the limits of counterfactual argumentation: if we knew exactly about the ratio of gain to risk, the problem would already have been solved, because we would then have already tampered with the germline *in vivo*, as I pointed out earlier; but this exactly is what is categorically prohibited.

Nossal: The question of the role of genetic information in mate selection is a real one. I understand that a great deal of work has been done in Greek villages, where the incidence of the sickle cell trait is very high and where arranged marriages are still common, to investigate whether it would be feasible to tell a person that he or she is a carrier and should therefore marry a non-carrier of that trait. I think the experience has been that mate selection has *not* been affected, even though antenatal diagnosis has. Is that correct?

Motulsky: George Stamatoyannopoulos of our department carried out these studies. In these Greek villages there was a high frequency of the heterozygous sickling trait. Several villages where marriages are arranged were tested. Although efforts were made to keep the results confidential, the families did find out who had the sickling trait and trait carriers were not considered desirable marriage partners. The outcome of the screening therefore was unfavourable in that carriers were stigmatized, even though the offspring of marriages between carriers and normals would be entirely normal clinically.

Williamson: The experience does differ from group to group. In Cyprus and in Sardinia, where the information on carrier status for thalassaemia became available *concurrently* with the ability to do prenatal diagnosis and to offer termination of affected pregnancies, the 100% response in those cultures has been to marry whom you like, and then to have the prenatal diagnosis. I believe, however, that in the New York Ashkenazi Jewish community, scientists hold test results for carrier status for Tay-Sachs disease. The rabbi asks whether those who are to be married (marriages are usually arranged) are carriers, and if the

answer is that two carriers are to marry, the marriage is not proceeded with. I think this is the only community where directed marriage occurs on genetic grounds.

Brenner: It's premarital counselling!

Williamson: Of a particularly draconian sort, yes.

Kuliev: On the question of whether attempts to influence marriage behaviour have been successful in the efforts to prevent genetic disease, the answer is probably that they have not, as we do not have any examples of this in ongoing programmes for genetic disease. There has been no significant success in reducing the frequency of consanguineous marriages, in Moslem communities, to avoid recessive conditions in the offspring. The more appropriate approach would seem to be to provide diagnostic services in communities with consanguineous marriages so that the birth of affected children is avoided, rather than to try to influence the choice of a marriage partner.

WSJ 3/8/89

Fraud vs. Error: The Dingelling of Science

By Bernard D. Davis

The recent interest of Congress in fraud in science is justified, because in a number of serious cases our academic institutions have responded very badly. We scientists have an even stronger interest in seeing this problem handled better, for we build our whole enterprise on a foundation of communal trust. Unfortunately, the congressional inquiry has become a crusade, punitively pursuing one of the most distinguished and productive biomedical scientists, David Baltimore of the Massachusetts Institute of Technology.

Last spring Rep. John Dingell (D., Mich.) held a subcommittee hearing on fraud in science, with the stated goal of preventing waste of tax money. He heard not only about several real cases, but also about a very shaky one. A postdoctoral fellow who had resigned (and quit science) questioned the veracity of the data in a paper written by her mentor in collaboration with Mr. Baltimore. This paper, on the effect of introducing a gene for forming a specific antibody into the fertilized eggs of mice, was exceptionally complex and also exceptionally interesting, for it concluded that in these "transgenic" animals the introduced gene and the host's genes did not act independently but interacted in altogether unexpected ways.

The congressional hearing had several serious faults: It blurred the crucial boundary between fraud and normal error; the dispute was far too technical for such a forum; and there was no opportunity for the accused to rebut the charges by the aggrieved witness. Major scientific organizations registe. protests. But Mr. Dingell had hooked big fish, with a Nobel Prize.

The National Institutes of Health (NIH) set up an outside committee of experts to examine the issue. Its report cleared the authors of any charge of misconduct, found errors of varying magnitude, and concluded that these did not undermine the main conclusions of the paper. As is usual, the draft report was submitted to the interested parties for correction and clarification. It led the authors to publish a retraction of the errors that they considered most significant.

Mr. Dingell might have been pleased at this outcome, and might even have expressed regret for the earlier implication of fraud. But his response was vindictive: a furious letter, protesting that the NIH had "defus" his issue by stimulating a premature traction, and demanding that the inspecto general of the governing department in estigate possible criminal actions.

In addit n, while Mr. Dingell could no longer hold his big fish on the suspicion of fraud, in a recent report of his subcommittee he presents a new goal: not to save tax money, or even to investigate misconduct (a broader term that has replaced "fraud" in most discussion), but "to ensure the continuing pre-eminence of American science." The door is thus opened for well-intentioned but clumsy interference of unlimited scope—abandoning the centuries-old recognition that science flourishes best if scientists are given broad latitude in ordering their own affairs.

Specifically, Congress has now suggested that an Office of Scientific Integrity be established, and that it audit scientific records on a random basis. But such auditing could rarely detect falsification in scientific records, which are very different from financial records. Moreover, in science nature is the ultimate auditor, and so the level of fraud is unusually low; hence random scrutiny would not be cost-effective.

If, on the other hand, the auditing sought errors, it would be useless: Inconsistencies in raw scientific data (as in the Baltimore case) are inevitable and require judgment by the investigator; hence science has developed well-tested methods for either correcting important errors or bypassing minor ones, ultimately building a solid edifice. Above all, the atmosphere created by auditing would erode the morale of scientists, discourage the recruitment of bright young students, and encourage institutions to overreact.

Such overreactions are already at hand—for example, the dean of Harvard Medical School dismissed a distinguished tenured professor for plagiarism though it was only the minor form of this offense, copying paragraphs in a review without rewording, rather than the serious form that falsely claims credit for discovery. In the Baltimore case, with no base of misconduct, we find another form of overreaction. The NIH committee criticized the authors for retracting only part of the uncovered errors, and the NIH administration now requires them to publish a retraction of all the others, including even clerical ones.

This decision is regrettable. It deprives a distinguished scientist of his right to exert judgment about what is a significant error, and to have the outcome of a dispute determined in the traditional way by further work, rather than by legal pressure.

Moreover, the NIH documents made no effort to focus on the broader implications of this degree of interference for the future atmosphere and style of scientific research. One can see why the NIH would take this position, for otherwise one can imagine the headline, "NIH Condones Error in Science." But the effort to avoid it has given an unfortunate message. It encourages legislators to delve into affairs where they cannot be helpful. And it encourages scientists to do more pedestrian work, rather than face the increased risk of mistakes when they explore challenging problems and push methods to their limits.

The attack on the Baltimore paper has already cost a great deal of money, has damaged the image of science on the flimsiest of grounds, and has been a tragedy for most of the participants. Moreover, Mr. Dingell has clearly intimidated scientists into dealing with the problem within his frame of reference, rather than that of the traditions of their profession. How far will this process go? Neither science nor society will benefit from a paralytic legislative crusade for an unattainable degree of purity.

Mr. Davis is an emeritus professor of bacterial physiology at Harvard Medical School.

THE WALL STREET JOURNAL.

11/17/90

THE GENETIC REVOLUTION: Scientific PROSPECTS AND Public PERCEPTIONS

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Contributors to The Genetic Revolution: scientific prospects and public perceptions

Bernard D. Davis, M. D. Adele Lehman Professor of Bacterial Physiology Emeritus, Harvard Medical School. Member Nat. Acad. Sciences.

Allan Campbell, Ph. D. Professor of Biology, Stanford Univ. Member Nat. Acad. Sciences.

Simon Levin, Ph. D. Professor of Ecology and Evolutionary Biology, Cornell Univ. Member Nat. Acad. Sciences.

Margaret Mellon, Ph. D. National Wildlife Federation.

Aaron Wildavsky, Ph. D. Professor, Political Science, U. Calif. Berkeley.

Charles Arntzen, Ph. D. Deputy Chancellor, College of Agriculture, Texas A & M Univ., College Sta., TX. Member Nat. Acad. Sciences.

Frank Loew, D. V. M. Dean, Tufts Univ. College of Veterinary Medicine.

Theodore Friedmann, M. D. Professor of Pediatrics and Genetics, Univ. Calif. at San Diego Med. School.

James Schwartz, M. D. Professor of Neurobiology and Member, Howard Hughes Center, Columbia Univ. Med. School.

Francisco Ayala, Ph. D. Professor of Ecology and Evolutionary Biology, Univ. Calif. at Irvine. Member Nat. Acad. Sciences.

Henry Miller, M. D. and Ph. D., Office of Biotechnology, US Food and Drug Administration.

Richard Stewart, Professor, Harvard Law School. (At present US Asst. Attorney General.)

Harvey Brooks, Ph. D. Emeritus Professor of Applied Physics, Harvard Univ. Currently at JF Kennedy School of Government, Harvard. Member National Acad. Sciences and formerly chairman of its Committee on Science and Public Policy (COSPUP)

[D. Davis, ed.: The Genetic Revolution]

[Draft 11-20-90]

PREFACE

In a world surfeited with hyperbole the word revolution readily evokes skepticism. But if it is ever a useful term, to characterize a fundamental change in our outlook or our powers, it surely applies to molecular genetics as much as to the earlier agricultural, industrial, Copernican, and Darwinian revolutions.

The genetic revolution was foreshadowed by two great discoveries. After decades in which classical genetics could deal with genes only as purely formal units of inheritance, in 1944 Oswald Avery, Maclyn McCarty, and Colin MacLeod showed, most unexpectedly, that the material substance of the gene is deoxyribonucleic acid (DNA). Nine years later James Watson and Francis Crick launched the field of molecular genetics by discovering that DNA is composed of two complementary strands -- a remarkable structure that immediately accounted for the ability of genes to replicate information in successive generations. The rapid growth of molecular genetics then yielded, within a mere 20 years, the revolutionary ability to alter genes at will in the test tube, and to insert them into any organism.

This development, called genetic engineering, has provided enormously powerful tools to virtually every field of biological and medical research and to a rapidly expanding biotechnology industry. In addition, in the study of evolution -- the unifying theme of the life sciences -- molecular genetics provides deep new insights into mechanisms, as well as powerful new ways to determine and to time the branching lines of descent in the four billion years between bacteria and man.

However, along with great expectations, genetic engineering has generated concern about our ability to handle the new manipulative and predictive powers wisely, and also anxiety about possible risks. Here the public is treading on unfamiliar ground, where it finds it hard to know whom to trust. In particular, the introduction of genetically engineered organisms into the environment, for agricultural or related purposes, has given rise to a most unusual controversy within the scientific community. Microbiologists and molecular biologists are eager to test promising recombinants derived from familiar, harmless organisms; but for many ecologists, concerned with any changes in the distribution of organisms in the environment, the novelty of the recombinants is a cause of concern that would justify considerable delays in testing. Although all agree that the risks have a low probability, the differences in emphasis have made it difficult for our regulatory agencies to agree, even after several years, on a consistent set of regulations, or on definitions for harmless classes of organisms that might be exempted.

In its applications to humans molecular genetics also raises different kinds of problems. One is defining the moral limits of gene therapy and its possible shading into eugenics. Another is created by our increasing ability to detect genetic susceptibility to various diseases. For this knowledge, intended to benefit individuals, also may be used to invade their privacy, or to burden them with discouraging predictions that they might not want.

This book is intended to provide assessments by highly qualified experts on various aspects of the problems raised by the genetic revolution. To lay readers the prospect of such a book, with chapters by many different authors, may seem discouragingly academic. But since the problems of genetic engineering have already been extensively debated it seemed that if a further contribution were to be valuable it would have to dig deeper than most comprehensive discussions, and so it would require highly professional, sophisticated analyses of the various topics. At the same time, we have made every effort to ensure a style that is accessible to lay readers.

The book is organized in the following way. The first chapter discusses the key issues. The next, on the origins of molecular genetics, portrays a remarkable intellectual triumph, of interest in its own right and as a model for future growth of the field. In addition, this chapter provides a vocabulary for the subsequent scientific chapters, which discuss where we now stand, and where we are likely to go in the near future, in applying the new techniques to microbes, plants, animals, and humans, and to the understanding of evolution.

The rest of the book focuses on public perceptions and governmental responses, and on the factors that influence them. These chapters provide a variety of perspectives, coming from environmentalism, the law, political science, and governmental regulation. But along with some conflicting views there is agreement that wise policy must balance the likelihood and the magnitude of the benefits and the dangers, rather than seek an unattainable zero risk. There is also agreement on the need for

better public education on the relevant science -- especially recognition that only a tiny fraction of microbial species cause disease, while the vast majority have beneficial and even indispensable roles in the cycle of life.

Two closing chapters provide a summary, with critical commentary. For those readers who find some of the scientific chapters too detailed the summary of their high points in the chapter by the editor (Ch. 14) will provide an adequate background for the chapters on policy. In the final chapter Harvey Brooks, a physicist long engaged in problems of public policy, comments on the chapters that bear particularly on this aspect of the subject. This discussion will bring out interesting similarities between policy problems now encountered in genetic engineering and those that arose earlier from the physical sciences.

Finally, although the controversies over the regulation of engineered organisms are still not settled, there is little doubt that biotechnology will flourish. Yet it is likely also to face a continuing challenge in trying to minimize the waste effort and delay caused by accommodation to public perceptions that do not distinguish real problems from excessively remote possibilities. We hope this book will illuminate these issues for a wide audience of concerned citizens, as well as biomedical scientists and government officials. It may also provide a useful paradigm for future novel intersections between science, technology, and society.

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Preface
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The American Academy of Arts and Sciences sponsored this book, including a conference of the contributors. The book is in a sense a specialized continuation of an earlier publication of the Academy, "Progress and Its Discontents" (edited by G. A. Almond, M. Chodorow, and R. H. Pearce, University of California Press, 1982). Related topics have also been taken up in several issues of the Academy quarterly Daedalus: Science and Its Public: the Changing Relationship (Summer, 1974); Limits of Scientific Inquiry (Spring, 1978); Modern Technology (Winter, 1980); Scientific Literacy (Spring, 1983); America's Doctors (Spring, 1986); Art and Science (Summer, 1986); Risk (Fall, 1990).

We are very grateful for generous financial support from the Lucille P. Markey Charitable Trust, the MacArthur Foundation, and the Rockefeller Foundation, and for assistance from the staffs of both the American Academy of Arts and Sciences and the publisher. Virginia LaPlante provided valuable editorial advice.

Bernard D. Davis

PERSPECTIVES IN BIOLOGY AND MEDICINE

Editor: RICHARD L. LANDAU

BOOK REVIEWS

Storm over Biology. By BERNARD D. DAVIS, Buffalo, N.Y.: Prometheus Books, 1986. Pp. 324. $22.95.

This is a collection of essays on public and academic policy written, not by a sociologist as one might guess, but by a distinguished microbiologist and geneticist. Whereas the sociologist would probably have written such articles with feigned detachment, Davis's "objectivity" is tinged with quiet good-humored passion and thus carries a real punch. These essays defend the objectivity of biological science with courage and effectiveness. Fortunately, he wrote well and obviously enjoyed the verbal encounters he entered. Most of the articles and editorials were originally published in scientific journals, but several appeared where they would be read by the educated general public to whom he was also appealing. Short explanatory paragraphs point to the detailed relevance of each article and help maintain a continuing story. Some of these articles were written 15 years ago; all of them are as pertinent today as when they first appeared.

A card-carrying liberal, Davis was accused of bigotry and intolerance by a few Harvard faculty colleagues for defending efforts of investigators to attempt to develop methods for measuring intellectual ability. He supported the concept of sociobiology and in doing so sustained the label of a racist. Antiscientists attacked him for defending molecular genetic research and the technical application of these remarkable advances. He understood the fear generated by the rapid advances in this area and was persuasive in advocating caution and reasonable safeguards. He appreciated that pushing ahead without educating the public could, if accidents occurred, lead to the loss of its support. It is important to appreciate that in none of these positions was Davis defending his own research but, rather, the scientific community.

He also demonstrated in one essay that he had the courage to act against his own university when, under the leadership of the dean, academic standards were discriminatorily lowered for some students. Here again he was bitterly maligned for his efforts to ensure that a great university did not lower its standards for selected students. To the shame of the rest of the medical school faculty, he found himself almost alone on this issue. Having tenure did not provide courage for many of his colleagues who confidentially sided with him on the issue.

This review, appearing several years after publication of the book, is appropriate, because Davis has drawn the issues clearly, and they are timeless. It may well be that his vigorous and articulate stands are partially responsible for the fact that science and academic scholars remain as free as they are in 1990.

THE WHITE HOUSE

WASHINGTON

March 26, 1991

Dear Professor Davis:

Many thanks for your letter of March 15.

The points you make are, of course, very much well taken and I have read with interest the material that you have provided with your letter. I also would admit that in drawing the distinction between opportunities and entitlement, I obviously was making the picture an extreme one to emphasize my point and to draw attention to what I feel have been rather counterproductive activities, both in the medical field and the physical sciences recently on the entitlement front. I could not agree with you more, however, that promising immediate returns from fundamental research is not only dangerous, but actually dishonest.

Many thanks for writing and for sending me such interesting material.

With warmest best wishes,

SIncerely yours,

D. Allan Bromley
Assistant to the President
for
Science and Technology

Professor Bernard D. Davis
Bacterial Physiology Unit
Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

Dear Sir -

I have a BS in chemistry and almost enough grad work in biochem for an MS. I am currently, head chemist (basicly GC man) at US Transformers in Jordan. Did my thesis on PCB-induced brain damage, so I know something about toxic chemicals.

Saddam Hussein is said to have lots of nerve gas, mustard gas, and so forth, which he might use on our troops. Presumably you are working on countermeasures.

If you can use a slightly-out-of-practice biochemist / fairly good GC man, give me a call.

Sincerely,

Joe Smith
PO box 98
Jordan, Minn
55352
612-492-2720

PS I am not looking for a permanent position - am offering to help out primarily during war.

JDS