Biotechnology : professional issues and social concerns / editors, Paul DeForest [and others].

Contributors

DeForest, Paul.
AAAS Committee on Scientific Freedom and Responsibility.

Publication/Creation

Washington, DC : American Association for the Advancement of Science, Committee on Scientific Freedom and Responsibility, [1988], ©1988.

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Professional Issues and Social Concerns

Editors

Paul DeForest ✦ Mark S. Frankel

Jeanne S. Poindexter ✦ Vivian Weil

American Association for the Advancement of Science

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October 1988

American Association for the Advancement of Science
Committee on Scientific Freedom and Responsibility

The Committee on Scientific Freedom and Responsibility is a joint committee of the AAAS Board and Council. The committee was created in 1976 to develop policies and procedures to protect scientists and engineers against infringements of scientific freedom and responsibility, to maintain an awareness of actions by governments which might affect the professional rights and duties of scientists and engineers, and to develop programs to foster attention to scientific freedom and responsibility within AAAS and its affiliated societies. The Committee's activities are organized into three program areas: Professional Ethics, Science and Society, and Science and Human Rights.

The preparation and publication of this monograph was supported by grants from G.D. Searle and Company and the Monsanto Company.

The views presented in this publication are those of its editors and authors, and should not be attributed to the Board or the Council of the American Association for the Advancement of Science or to G.D. Searle and Monsanto.

AAAS Publication 88-23

Preface

Mark S. Frankel
American Association for the Advancement of Science

Biotechnology research and development are the focus of considerable public attention these days. And why not? The ability to alter genetic material to achieve desired outcomes in living organisms promises to change the way we live in dramatic ways. Some of the outcomes predicted for human health, agriculture and the environment can only be described as revolutionary. It is not surprising, then, to find such heightened interest in biotechnology from so many different quarters.

In a report analyzing the current level of support for biotechnology by federal and state governments and the private sector, the U.S. Office of Technology Assessment (1988b) found that the federal government spent $2.7 billion in fiscal year 1987 in support of biotechnology research and development, that the states invested $147 million in such research and development in the same year, and that American industry spends $1.5 - 2.0 billion annually to promote biotechnology research and development. The report noted that approximately twelve federal agencies, 33 states, and more than 400 U.S. companies are supporting biotechnology research and development. The U.S. Congress (Subcommittee on Toxic Substances and Environmental Oversight, 1986; Subcommittee on Investigations and Oversight, Subcommittee on Natural Resources, Agriculture Research and Environment, and Subcommittee on Science, Research and Technology, 1986) has convened hearings on biotechnology, the Office of Technology Assessment (1987; 1988a; 1988b) has issued several reports on new developments in biotechnology, the prestigious National Academy of Sciences (1987) has published a report of a special committee established to assess the debate over the introduction of genetically engineered organisms into the environment, and the press has been prolific in its coverage of biotechnology issues (e.g., Schneider, 1987; Gladwell, 1988; Freudenheim, 1988).

This virtual explosion of interest in biotechnology is fueled by several anticipated consequences. Biotechnology's potential to advance the nation's health, contribute to the food supply, and improve environmental quality are benefits that all would welcome. Indeed, a "large majority of the American public (82 percent) believes that research in genetic engineering and biotechnology should be continued. Support...appears in all segments of the population" (Office of Technology Assessment, 1987, p.5). The promise of increased employment opportunities, financial profit and improving U.S. international economic competitiveness motivates a great deal of government and industry investment in biotechnology research and development. But not all of this mounting interest in biotechnology has been precipitated by perceived benefits. Indeed, much of the national dialogue on biotechnology reflects an uneasiness among many in our society over the possible harms associated with biotechnology research and development. Two of these latter concerns – the consequences of increased industry-university collaboration and the safety of biotechnology research – are the focus of this volume.

At the February 1987 AAAS Annual Meeting in Chicago, the AAAS Committee on Scientific Freedom and Responsibility co-sponsored two symposia on biotechnology and the papers presented there constitute the bulk of the essays that follow. Additional

papers were included when it was thought that they would bring a needed and useful perspective to the consideration of key issues.

The papers in Part I consider the topic of "Assessing Corporate-Academic Ties in Biotechnology." As these papers document, collaboration between universities and industry has played an important role in biotechnology research, with nearly half (46%) of all biotechnology companies supporting research in universities (Office of Technology Assessment, 1988b, p.113). For industry the benefits of such collaboration include access to top university researchers and their students, training opportunities for company scientists, reduced costs of conducting R&D programs in a new field, improved public image, and advantageous licensing arrangements. For universities the benefits are a new source of research funding, involvement of faculty and students in frontier areas of applied research, and direct participation in the transfer of research to product development.

Yet such collaboration has also prompted concerns about its impact on the values and mission of universities. These concerns, in one form or another, have encompassed issues of academic freedom, conflicts of interest, the university's public service role, propriety information and publication, the research priorities of faculty, and possible constraints on the education of students.

In response to these concerns, most universities whose faculty are involved in collaborative research have adopted institutional guidelines governing such agreements. The Office of Technology Assessment (1988b, p.20) recently reported that "most parties continue to be optimistic about the goals of these relationships and are more comfortable with them than they were 10 years ago." But recognizing that the effects of such university-corporate ties may be evolutionary and cumulative, the Office of Technology Assessment, noting that the "debate over the impact of such collaboration on academic science remains unresolved" (1988b, p.6), contends that "the situation warrants monitoring. There remains sufficient concern about the long-term effects of such funds on research agendas, secrecy, conflict of interest, and student education" (1988b, p.7). In this spirit, the papers in Part I, whose authors represent both industry and university perspectives, acknowledge successful university-corporate arrangments, but they also elaborate from different vantage points on the concerns reported on in recent reports, cautioning us to remain alert for adverse effects on important values and pragmatic ends.

In Part II, attention is focused on the "Responsible Uses of Microorganisms and Microbiological Products." In pursuing a number of potential applications of biotechnology, the accidental or intentional release of genetically altered organisms into the environment may occur. While scientists continue to clash over the nature of the risks associated with such releases or even how to assess them (see, for example, the Policy Forum in *Science*, 1987), the public is "sufficiently concerned about potential risks that a majority believes strict regulation is necessary" (Office of Technology Assessment, 1987, p.5).

These differences among scientists and the level of public concern have had several effects. Some experiments have been substantially delayed as uncertainty about risks has led to public protests and prolonged litigation (Schneider, 1987). In this country, regulation of biotechnology has proceeded spasmodically at the federal level and still creates confusion among researchers (Strobel, 1987). A "patchwork pattern of local laws" (Gladwell, 1988, p.H5) may be emerging at the local level which will only add to the confusion. And since microorganisms do not recognize national boundaries, there have been calls for international guidelines on dissemination of new organisms (Dixon, 1988).

The controversy over the potential hazards of genetically engineered organisms is unlikely to dissipate in the near future. The papers in Part II contribute to the ongoing national dialogue on this issue. Three of those papers are by scientists engaged in biotechnology research and development who describe scientific work now underway and explain why any risks associated with those efforts are likely to be minimal. Excerpts from a recent report of the Office of Technology Assessment (1988a) are also included in order to bring a more "public" perspective to bear on the issues.

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Preparation of this monograph benefitted from the contributions of many people. Special acknowledgement goes to the authors of the papers appearing in the volume and to my coeditors, who were organizers of the two symposia in Chicago and who were responsible for securing the papers for their sections of the monograph. Amy Crumpton of the AAAS Office of Scientific Freedom and Responsibility very ably assisted me in the production end of this effort.

All of those involved in the project gratefully acknowledge the financial support of G.D. Searle and Company and the Monsanto Company which made the publication and wide dissemination of this volume possible. Neither corporate sponsor was involved in organizing the original symposia or in preparing the papers for publication.

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PART I

Assessing Corporate-Academic Ties in Biotechnology

Contributors

Roger N. Beachy is Professor of Biology at Washington University in St. Louis and best known as the producer of the world's first genetically engineered food crop resistant to disease. His technique to produce tobacco mosaic virus resistance in tomatoes has been repeated by other researchers to produce plants resistant to other diseases. Beachy has travelled the world as a lecturer on plant biology and genetic engineering research. He is a member of the American Society for Plant Physiology, American Phytopathological Society and the American Association for the Advancement of Science, among other organizations.

Michael Davis, a philosopher, has taught at the University of Michigan, Case Western Reserve University, Illinois State University, and the University of Illinois at Chicago before coming to the Illinois Institute of Technology in 1986 as Senior Research Associate at the Center for the Study of Ethics in the Professions. Among his publications concerned with ethics, political philosophy, and philosophy of law is a recent monograph, *Conflicts of Interest in Engineering.* He held a fellowship from the National Endowment for the Humanities for the academic year 1984-85.

Paul DeForest is Associate Professor of Political Science at Illinois Institute of Technology. His most recent publications in the area of biomedical policy is "Bureaucracy in Biology: the Struggle to Control Postwar Biomedical Research," in *Biology and Bureaucracy,* edited by Elliot White and Joseph Losco (1986). He is currently engaged in a study of European Community biotechnology policy.

Clifford Grobstein is Professor Emeritus in the Program in Science, Technology and Public Affairs at the University of California, San Diego. He is an embryologist, that is, developmental biologist, concerned with reproductive biology and development in humans. His new book, *Science and the Unborn,* deals with the problem of assigning appropriate status to the unborn in connection with in vitro fertilization, surrogacy, therapeutic transplantation of fetal tissue, and fetal surgery.

Sheldon Krimsky, a philosopher of science, is Associate Professor in the Department of Urban and Environmental Policy at Tufts University. He is the author of *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* and the co-author of the forthcoming book *Environmental Hazards: Communicating Risk as a Social Process*. His essays have appeared in the *American Journal of Public Health*, the *Bulletin of the Atomic Scientists*, *Environment*, *Science, Technology & Human Values*, the *American Scientist* and many books. He serves as chairperson of the Committee on Scientific Freedom and Responsibility of the American Association for the Advancement of Science for 1988.

Edward L. MacCordy is the Associate Vice Chancellor for Research for Washington University. The responsibilities of his present position include research and sponsored program policy making, development of external support and relationships, administration of sponsored programs, and management of the transfer of technology. He is a Fellow of the National Academy of University Research Administrators, a past president of the National Council of University Research Administrators, a Vice President of the Society of University Patent Administrators, a Board member of the Council on Governmental Relations, and is active in the Licensing Executives Society.

Jeffrey S. Price joined Cetus Corporation in 1976, and has held a series of research positions, including responsibility for the company's entire R&D function in 1982 as Vice President, Research and Development. He was appointed Senior Vice President in July 1986. In his early years at Cetus he headed several innovative programs developing multi-enzyme processes as well as pharmaceutical process strain and productivity improvements. His first assignment with Cetus was as a scientist responsible for molecular and microbiological research.

Vivian Weil, a philosopher, is Director of the Center for the Study of Ethics in the Professions and Associate Professor of Ethics at the Illinois Institute of Technology. Her applied work focuses on issues of ethics and social responsibility in engineering, science, and business. She has organized research on controls on the flow of scientific information. Her most recent publication is "Policy Incentives and Constraints on Scientific and Technical Information," in the October 1988 issue of *Science, Technology, & Human Values*.

Industrial Support of University Biotechnology Research: An Introduction to the Issues and Perspectives

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The "new biotechnology" has been defined as the development and industrial use of novel techniques stemming from the revolution in genetic engineering, including recombinant DNA and cell fusion (OTA, 1984, p.3). As this definition suggests, commercial biotechnology encompasses two interrelated revolutions. One is the revolutionary impact of biotechnology, to date primarily a revolution of expectations, upon medicine and human health, agriculture and food production, energy and the development of new and more efficient fuels, and so on. The other is the purported revolutionary narrowing of the time interval from basic research discoveries to the commercialization of production.

The societal impact of the new biotechnology became a subject of debate in the mid-1970's when public concern arose over the need to restrict or regulate recombinant DNA research. Some of the immediate risks cited by critics, for example, those posed by release of laboratory recombinants, were early on subjected to assessment. Other risks were remote, awaiting the production of recombinants on an industrial scale or advances in genetic knowledge and control as yet beyond the capabilities of scientists. By the early 1980's, the immediate risks had been judged acceptable, at least by most scientists, corporate officials, and policy-makers. As commercialization accelerated, attention shifted to the need to anticipate and guide the social and economic impacts of biotechnology: to ensure global equity in access to products; to protect the interests of farmers and breeders; to guarantee that "orphan drugs" directed toward health problems affecting only small numbers of individuals or toward diseases concentrated in the underdeveloped world would not be ignored. Although concerns about the risks of genetically engineered organisms to the environment, human health and social values continue to be raised, a separate set of concerns has emerged, focusing on the impacts of biotechnology research on the institutions which sponsor and conduct the research.

The papers in this part are concerned primarily with the impact of corporate support of biotechnology research on the universities which conduct the research and on their faculties. Donald Kennedy, biomedical scientist and president of Stanford University, asserts that the "revolutionary compression of the trajectory of innovation" characteristic of the new biotechnology has brought to an end the long separation between fundamental research, concentrated in universities, and its commercialization, controlled by private firms (Kennedy, 1982). While academic-corporate linkages can be traced to the turn of the century, the incorporation of basic research itself into the production cycle is a more recent development.

The increase in government support of university scientific research following World War II can provide a useful perspective on current issues surrounding corporate-univer-

sity research relationships. The commitment by the federal government to exponential growth in funding basic scientific research certainly qualifies as a "revolution" (England, 1982). In 1940, the federal government provided about $15 million for university research and development, primarily in agriculture. Within two decades, federal support had escalated to about $400 million, including $100 million channeled through the National Institutes of Health. Meanwhile, industrial support of university research and development grew much more slowly, reaching only about $40 million by 1960. The trend continued during the next decade; as federal funding accelerated, the share provided by industry declined from ten to about three percent.

Robert M. Rosenzweig, president of the Association of American Universities, recently asked why, given the clamor which has greeted growing industrial support of university biotechnology research, no alarm was sounded over the much greater dependency caused by the earlier, and continuing, massive federal funding of university research (Rozenweig, 1988, p.3). In fact, concerns were expressed, often forcefully, over the possible skewing of basic research caused by federal emphasis on certain favored fields such as elementary particle physics, over the aggressive practice of pork-barrel politics by some scientists and university administrators, and over the potential threat to the viability of the burgeoning academic research establishment should federal funding eventually slow or reverse (Greenberg, 1967).

However, if the reaction then was relatively muted, that may be because scientists were loath to criticize the "basic research model" which governed postwar science policy. The federal government endorsed the notion that government funding of basic research promotes national security, welfare and economic growth. It accepted the principle of scientific autonomy, and surrendered control over distribution of research funds to the scientists themselves (Averch, 1985). On the rare occasions when the model was challenged, most notably during the Nixon administration's "War on Cancer," university scientists and administrators complained very loudly and government responded (Rettig, 1977).

By the late 1970's, however, the commitment of the federal government to meet the escalating needs of academic research was coming under increasing strain. Declining rates of economic growth and competing demands from other discretionary budget sectors caused federal support for basic research to drop below levels regarded by many scientists as necessary for continued vitality and expansion. Federal scientific and budgetary officials urged the scientific community to use available funds more efficiently and to set research priorities. Federal basic research emphasis shifted toward areas deemed vital to national security. In other areas, including biotechnology, where research and development could promote domestic productivity increases and enhance international competitive advantages, government emphasized its role as facilitator of increased cooperation between industry and academia (Dickson, 1984).

These changes in policy signaled a pulling back from certain central assumptions of the basic research model: that the advance of fundamental knowledge was a more valuable activity for scientists than product development; that federal funds were preferable to industry funds because there were fewer strings attached; that the profit potential from basic research was too low, too remote or too uncertain to justify sufficient corporate investment (Shapley and Roy, 1985). Biotechnology is considered an important test case of the implications of shifting government policy, industrial investment patterns, and academic values and expectations during the 1980's.

What lessons can be learned from fields which had earlier undergone a revolution in the relation between basic research and product development? An instructive com-

parison is suggested by the development and marketing of semiconductor diodes. Semiconductor theory can be traced to the beginning of the twentieth century, but its impact on the electronics industry awaited the invention of the transistor after World War II. Thereafter, however, progress was rapid. The electron tunneling effect, discovered in 1957, was being incorporated into marketable electrical diodes for computers and other devices using transistors by 1963 (Braun and McDonald, 1975).

A number of differences between the semiconductor and biotechnology industries are worth noting (OTA, 1984, app. C). One of the most important concerns the role of the federal government. In semiconductors, federal funding was justified not so much to advance fundamental knowledge as on grounds of national security (Levin, 1982). In contrast, the major breakthroughs in genetic engineering were accomplished through undirected federal research support.

A second important difference was in the pattern of academic-corporate relationships. University scientists were among the pioneers both in semiconductor research and in the exploitation of the technology's commercial prospects. When they decided to launch start-up firms, however, these academic entrepreneurs generally severed full-time university ties, although they located their firms near leading centers of academic research – for example, Route 128 around Cambridge, Massachusetts and the Silicon Valley near Palo Alto, California (Rogers and Larsen, 1984). In biotechnology, also, the research innovators were among the earliest to recognize the potential for commercial products and profits, often prodded by university patent officers. But biotechnology is probably unique in the extent to which scientist-entrepreneurs have managed to retain their full-time university posts. For a variety of reasons, including their attachment to academic traditions and culture, and their need for continued access to university laboratories, students and staffs, scientists have been reluctant to leave their universities. And their universities have been just as reluctant to let them go, seeing the opportunity for new sources of research support and training, as well as the profit potential from university owned licenses and patents.

Finally, there are differences in size and structure of the corporations active in these two fields. Of the many semiconductor firms spun off from university laboratories, a number eventually became major corporations. This process has been much slower in the case of biotechnology. Venture capitalists, many with scientific backgrounds, took an early interest in the field, seeking entry into what they believed would become a high technology growth industry. The New Biotehnology Firms (NBF's) extablished as partnerships between venture capitalists and university-based scientists have subsequently played a major role in the biotechnology industry, especially in innovation and product development. In manufacturing and marketing, however, limitations of size, capitalization, and expertise have led NBF's to negotiate agreements with established pharmaceutical, chemical, and other firms, often at the risk of takeover. As yet, there is no single corporation in biotechnology which has become both horizontally integrated, encompassing a range of product sectors, and vertically integrated, covering all stages of the research, development, production, and marketing cycle. Universities have been able to retain many of the most eminent scientists, as well as unrivaled laboratory facilities and well-trained support staffs.

The federal government has viewed the establishment and expansion of university-industry linkages in biotechnology as providing perhaps the best opportunity for the United States to translate acknowledged leadership in basic research into eventual dominance of a global marketplace (OTA, 1984, part III). Revision of tax laws to permit accelerated depreciation of investment and of patent laws to allow corporations and

universities to obtain patents for products developed through federally funded research are testimony to a shift in policy toward reliance on the talent and creativity of university researchers, and on the entrepreneurial and marketing skill of U.S. firms. In contrast to the centralized, government-directed strategies followed by Japan and urged by the European Commission, the U.S. government remains committed to a pluralistic, free enterprise approach toward international competition in biotechnology.

University-industry research relationships (UIRR's) are seen as a key American asset. Whether as the result of the natural matching of complementary resources and capabilities or of government encouragement and incentives, industrial support of academic biotechnology research has undergone dramatic growth in the 1980's. This growth has been more rapid than industrial support of scientific research in general. While the federal government remains the largest source of funds for biotechnology research, a growing number of university faculty working in biotechnology report receiving significant support from corporate sources (Blumenthal et al., 1986b).

The forms assumed by biotechnology UIRR's have been influenced by the legacy of academic-corporate contacts in other fields, as well as by circumstances and needs unique to biotechnology. In general, two major categories of linkages have been established: those between individual faculty researchers and their financial backers; and those which are negotiated institution-to-institution by university administrators and corporation officials. Industrial funding of individual faculty researchers and part-time faculty consulting with industry are well established practices in science and engineering, generally accepted and even encouraged by universities. What is most striking about biotechnology, however, is the extent to which leading university faculty have assumed major equity positions in biotechnology firms, as reflected in the annual list of biotechnology millionaires compiled by *Genetic Engineering News*.

The pattern of institution-to-institution relationships is also much the same in biotechnology as in other scientific and techical fields. The only truly innovative form, university sponsorship of biotechnology start-up firms, has had a decidedly mixed record to date. The most ambitious attempt, by Harvard University, was abandoned due to strong faculty opposition to the idea of Harvard going into business, as well as serious personal doubts by its president (Bok, 1981). The one firm which has been launched, Neogen, furthered a deliberate strategy by Michigan State University administrators to retain biotechnology faculty. Other forms of UIRR's, such as research contracts, industrial affiliates programs and arrangements providing entry to university laboratories for corporate scientists, have long existed in other fields, but have recently grown rapidly in biotechnology. The most widely noted cases have been the decisions by domestic and foreign corporations to endow entire departments (for example, the Hoechst Department of Molecular Biology at Massachusetts General Hospital), to create new institutes or centers (for example, the Whitehead Institute at MIT), or to secure first right to commercial exploitation of research across a university campus (for example, the arrangement between Monsanto and Washington University).

Unsurprisingly, corporations funding university biotechnology research are quite satisfied with the results so far and the prospects for the future, and see few serious problems. Industry has gained access to the best facilities and talent available, under acceptable terms, with substantial license, patent, and profit benefits (Blumenthal et al., 1986a) Although industrial funding is also attractive to universities and faculty because it provides the capability to expand research facilities, add staff, support graduate students, and increase revenues, a number of potential risks have been recognized.

One major concern is over the risk to academic values and relationships originating in corporate support of individual university researchers. According to some respected scientists, equity participation has promoted secrecy, rivalry, jealousy, the exploitation of students, and the neglect of academic duties (Novick, 1987). The extensive survey of biotechnology faculty directed by David Blumenthal provided little concrete evidence to support this charge. The Blumenthal team found a positive correlation between industrial support and both research productivity and professional activities, and no measurable negative impact on either teaching or university service. Only a tiny number of respondents reported that they held equity positions in firms which also supported their university research. However, the team cautioned that equity holdings may have been underreported due to their sensitivity. Moreover, a large percentage of biotechnology faculty receiving industrial support, and an even higher percentage of those who do not, cited serious potential risks, including excessive emphasis on applied research and commercial activities, increased secrecy and delays in publication, and reduced cooperation and collegiality among faculty (Blumenthal et al., 1986b).

There is also considerable concern over the threat to the mission of the university to educate students and advance fundamental knowledge posed by increasing dependence on corporate support. Clearly, it is neither desirable nor feasible for industry to accede to the same conditions which the federal government accepted for its support of university research. Areas of research having the greatest prospect of commercial advantage will be favored. Proprietary interest will often require secrecy or delays in publication. Given the crucial importance of science and the university to society, there are significant broader implications of industrial support of biotechnology which have attracted the attention of Executive agencies, Congressional committees and public interest groups, as well as scientific and university associations (Biddle, 1987; Mangan, 1987). Nevertheless, the initiative in the effort to minimize any threat posed by corporate ties to scientific freedom, the autonomy of science, and the integrity of the university must be taken by academic administrators and faculty.

The nature of the concerns, at once serious and difficult to substantiate, have led to repeated rounds of debate, with little progress toward resolution. The most enthusiastic supporters of corporate-academic ties acknowledge that there exist potential problems, but insist they are no greater in biotechnology than other fields subject to commercial interest, and probably less than fields subject to national security considerations. Even the purest of scientific fields, like mathematics and elementary particle physics, frequently manifest rivalry, secrecy, exploitation of graduate students, and charges of fraud. Yet the critics, including academic scientists not active in biotechnology, senior biologists defending traditional disciplinary values, and students of scientific research from the humanities and social sciences, warn that the threats are far more serious than acknowledged by university administrators and biotechnology faculty, and repeatedly cite specific cases of abuse (Kenney, 1986). The defenders argue in turn that such abuses are rare and their effects exaggerated, that UIRR's are working well on the whole, promising real benefits which greatly exceed any speculative risks, and that mechanisms have already been instituted to protect science and universities from any serious threats (Rosenzweig, 1988).

There is need for critical examination of the claims made by both sides, pointing out where the arguments are overdrawn, the conclusions unproven, the data inaccurate or misinterpreted (Feller, 1986). The surveys directed by Blumenthal have yielded important data but, as the authors point out, they have raised perhaps more questions than they have answered, questions which cannot adequately be dealt with by means of the

survey format. More detailed studies of specific cases of UIRR's and of concerns noted in the Blumenthal surveys would be most useful.

In the hope of advancing the debate, a symposium was arranged at the 1987 annual meeting of the American Association for the Advancement of Science to provide the perspectives and observations of participants from various sectors of the academic-corporate biotechnology complex. After each speaker had presented his views, the subject was opened for audience participation, questions, and general discussion. Subsequently, the speakers were asked to revise their presentations for publication, and the perspectives of two additional participants were invited. The product of this effort is the set of papers which make up this part. The authors of three of these papers, Roger Beachy, Edward MacCordy and Jeffrey Price, are by virtue of their special knowledge and roles in a position to provide first-hand reports about how these new arrangements are affecting the university and scientific research. The other three authors, Sheldon Krimsky, Clifford Grobstein and Michael Davis, take a wider view of the institutions in question. Krimsky analyzes the role and mission of the university and describes the threats to universities from the new arrangements in light of that analysis. Grobstein proposes a scheme for guaranteeing support of fundamental research while protecting universities' traditional distance from the marketplace. Davis attempts to clarify the debate by identifying two fundamentally distinct conceptions of science underlying the disputes and worries which have arisen. In a concluding paper, Vivian Weil suggests the need to examine the extent to which corporate support of university biotechnology research may be altering the traditional norms governing fundamental research in academia.

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The Impact of Proprietary Arrangements on Universities

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The research university is an institution caught up in a rapidly changing domestic and international environment. Increasingly it seeks to be an active participant in national and regional economies and of direct and immediate service to society, but without compromising its autonomy and traditions. This outward looking activism is driven by the prospect of new technology that will enrich lives and benefit the domestic economy. A natural outgrowth of university commitment to this activist role has been the establishment of an increasing number and variety of relationships with industry, for only through industry's development, production, and distribution resources can the benefits of technology conceived by academic scientists be delivered to society.

Some feel these relationships with industry are inherently compromising or pose the threat of grave consequences, as yet unrealized. But the dominant opinion in the academic community maintains that responsible conduct by faculty, together with thoughtful and cautious administration by institutional officials, can guide the research university through this era of increased service to society without degradation of academic traditions and processes.

This paper will begin with an examination of the major forces which impelled universities toward increased relations with industry. Next, the perceived threats to the university will be examined. The paper will conclude with an assessment of how well universities are adapting to this era of change.

Contributing Factors to Increased University-Industry Relations

Increased involvement with industry is a means to an end for universities, the end being the voluntary assumption of a more direct and active role in society. Five of the main factors which have influenced universities to follow this path are:

- a growing recognition of the debt owed the public for its massive and continuing financial support;
- federal encouragement to create and transfer new technology;
- opportunities for the immediate translation of new knowledge into practical use resulting from the accelerated pace of scientific discovery;
- the mushrooming of university-oriented state economic development programs; and
- the perception that industrial research funding is complementary to government support.

The research university's obligation to the public is derived from an unwritten social contract that for decades has maintained that massive financial support of academic research is provided in expectation of major benefit to society and the economy. Since World War II government financing has shaped the university research enterprise and

largely determined its composition and research priorities. Today, out of several thousand institutions of higher education, about 200 universities constitute the academic research enterprise, with 70% or more of its funding being provided by state and federal agencies. In 1985, federal R&D funds in excess of 6 billion dollars were awarded to these research universities.

The unwavering public belief in the research investment concept, that university R&D stokes the industrial engine, is evidenced by the maintenance of high government funding levels for academic R&D in spite of growing trade deficits, the decline of U.S. technological leadership, and a pressing need to balance the federal budget. In response to this expression of public confidence, universities have become more involved in the economy by means of increased activity in technology licensing, cooperative research with industry, and the establishment of incubator facilities and research parks.

A major federal study undertaken during the Carter administration, the Domestic Policy Review, identified as a national problem a "gap" between research universities and industry. It concluded that new knowledge and technology were not flowing from university research laboratories to U.S. industry to the extent needed and judged feasible.

Subsequently, Congress acted to provide new incentives by adding industrial research tax credits to the tax code and, establishing, in Public Law 96-517, a presumption of ownership by universities of patentable inventions produced by them under government sponsored research. This new ownership concept was a dramatic break with past practice, having the effect of eliminating government control of, or even involvement in, university technology transfer activities. This was a key element in establishing a research environment in the university attractive to American industry.

During this period advances in many fields of science and technology were accelerating and the time from discovery to application of new knowledge was shrinking dramatically. By far the most remarkable and promising scientific advances were those which provided the foundation for the new field of biotechnology. In rapid succession hybridoma technology was launched by Milstein and Kohler and recombinant DNA technology was developed by Boyer and Cohen. The commercial value of these new technologies was enhanced by the benchmark decision of the Supreme Court in the case of *Diamond vs. Chakrabarty* (1980), which for the first time in U.S. history allowed the patenting of novel living organisms.

The term "revolution" is used very sparingly in science, but in the case of biotechnology it seems appropriate. Even the most farsighted observers were unable to predict in advance the full impact these technologies are having on medicine, agriculture, and other fields. In the latter half of the 1980's it was evident that the biotechnology revolution was already having a major impact on the research university, its faculty, its research and training programs, and its technology creation and transfer activities. The licensing of biotechnology discoveries from academic laboratories is being encouraged by universities and aggressively pursued by companies.

In its formative years, the biotechnology industry found itself dependent on universities for both manpower and technology. Sensing boundless new commercial opportunities, companies, whether large or small, new or established, aggressively sought a variety of cooperative arrangements with knowledgeable, skilled, and innovative university researchers. Research universities willingly responded to the opportunities promised from active participation in an exciting science-based revolution of major potential benefit to society.

The importance of universities as a key source of technology in a lagging economy was not lost on state and local officials increasingly concerned with unemployment and deteriorating regional economies. In such states as New York, Pennsylvania, Ohio, Indiana, and California, regional economic development programs were launched to encourage their universities to contribute research resources to regional companies. State governments also assisted in the establishment of new university research centers, including but not limited to biotechnology, in the expectation that these centers would foster industrial growth by providing new technologies to aging industries burdened with outmoded products and processes.

One of the most interesting factors influencing university-industry cooperation is the host of new opportunities for challenging research to be found in such cooperation. Industrial support appeals to university researchers because it provides them with encouragement and freedom to go beyond the normal scope of their government funded projects. Federal and other non-commercial sponsors do not emphasize the generation of new technology because they have neither the mission nor the resources to translate discoveries into socially useful products and processes. Since most academic research support has traditionally come from these sponsors, it is not surprising that university researchers in the past concentrated on the expansion of the scientific knowledge base, rather than the practical application of new knowledge.

Recently, however, industry support has provided new opportunities to investigators to pursue the social applications of new scientific knowledge. Companies are providing funds to universities to extend the fundamental research projects supported by non-commercial sponsors with the hope and expectation that useful discoveries will result. Government agencies recognize the desirability of such complementary support and have developed special programs to encourage universities and their faculties to initiate industrial research alliances. The academic scientist has come to value such complementary industrial support because, in addition to contributing to the scientific knowledge base, his or her discoveries and ideas may now be developed to the point where they can be transferred to industrial laboratories, scaled up and produced, thereby providing direct benefits to society.

The research universities' increasingly activist role in the economy takes a number of forms. Prominent among these relationships in the field of biotechnology are the following:

1. **Faculty consulting**, a long established, personal, extracurricular professional activity, often praised as a means of technology transfer from the university, and second in effectiveness only to the matriculation of graduate students.
2. **Technology evaluation**, including clinical trials of experimental diagnostics and therapeutics, engineering evaluation of new materials, and field trials of experimental agricultural methods, equipment, plants, and chemicals.
3. **Licensing of intellectual property rights**, including patents on inventions, copyrights (mainly on computer software), proprietary materials (for example, unpatented hybridoma cell lines or genetically engineered organisms), and technical know-how legally entitled to trade secrecy status. Licenses may be exclusive to a single company or non-exclusively available to many companies, and may involve foreign as well as domestic rights.
4. **Research arrangements** of various types, including:
   - single projects having a sole principal investigator supported by one company;

- program consortia or centers usually involving multiple projects in a broad field of interest, multiple investigators directing these projects, and multiple industrial co-sponsors; and
- broad programs involving multiple projects and investigators, but sponsored by a single company and without any direct involvement by state or federal agencies.

Invariably, all of these research arrangements will have preferential technology licensing provisions for the industrial sponsors.

While universities have become more comfortable with their research relations with industry, it does not necessarily follow that they are also becoming increasingly dependent on industry for year-in and year-out research funding. Industrial support is not easy to attract nor does it represent a plentiful and stable source of funding covering the broad spectrum of long-term research. Instead, industrial sponsorship at research universities most often lends only partial support to a few top quality researchers, who remain primarily dependent on the successful competition for federal and other non-commercial support. By providing supplementary manpower, supplies, and instrumentation, industrial funding simply allows them to expand and deepen their primary investigations.

Perceived Threats to Universities

The recent expansion of university-industry research relations has been accompanied by widespread discussion of a set of perceived threats to faculty academic freedom and university autonomy as well as by questions concerning the ability to maintain established academic standards for personal conduct. The potential for conflict has been regarded as inherent in the cultural dissimilarities between profit driven, financial risk taking, hierarchically managed companies, on the one hand, and non-profit, financially conservative universities controlled by independent faculty members, on the other. A greater contrast in organizational objectives, policies, processes, practices, attitudes, and style would be difficult to find in society.

From this contrast there emerged a set of purportedly insurmountable problems standing in the way of greater industry-university cooperation. Prominent among these were:

1. **Research Selection**: To what extent should a company be allowed to define the research to be conducted with its funds?
2. **Direction and Control**: To what extent should a company direct and control the conduct of the university research it sponsors?
3. **Diversion**: Would industry influence cause a change in the balance of basic and applied research?
4. **Quality**: Would the quality of research decline as a result of replacing peer review with company evaluation and selection?
5. **Secrecy**: Should industry's desire to keep research results secret be allowed to restrict free dissemination to students, colleagues, and the scientific community? Would publication of graduate student theses and dissertations be placed in jeopardy?
6. **Company Preemption**: Would internal company R&D compete unfairly with that of universities, thereby denying faculty members the recognition and students the opportunities which result from their research and ideas?

7. **Ownership of Technology**: Should the sponsor who pays for research own the resultant technology? Might the university risk being a party to technology suppression? If ownership vests in the university should the sponsor receive an exclusive license? Should the licensed sponsor pay royalties? Who should file patent applications and be responsible for patent enforcement? Should the sponsor be entitled to ownership of chemical analogs and biological derivatives which it develops from university research results?
8. **Confidentiality Protection**: If the sponsor's proprietary information is used by university investigators should the university agree to enforce confidentiality? Would the company sponsor respect the confidentiality of unpublished university research plans and results?
9. **Faculty Conflicts of Interest**: Should the university be able to limit faculty consulting, research, and personal activities when necessary to protect the interests of a company sponsor?
10. **Full Cost Reimbursement**: Should company sponsors pay for the full direct and indirect cost of research or only the incremental costs of joining a well funded university research program?

A few years ago, the above were not only theoretical questions, but were hotly debated topics, reflecting widespread concern that industry's involvement in and influence over university research posed a serious and immediate threat to academic traditions, values, and objectives. Sensitive to the potential threat resulting from the differing cultures of industry and the academic community, universities and their faculties did not shrink from these problems but instead anticipated them, confronted them head-on and, for the most part, successfully resolved them in a manner reasonably acceptable to both their industrial sponsors and their internal constituencies.

The University-Industry Response

Admittedly, the process of adjusting to industrial support was not without some friction, as evidenced by such well publicized controversies as the reported misuse by a sponsor of a graduate student's research plan at the University of California at Davis, the faculty protest at Harvard over proposed institutional involvement in commercial activities, and the legal battle between the University of California and Hoffmann-LaRoche over ownership of the derivative of a cell line developed at UCLA.

The root cause of the aforementioned problems was the fact that universities and companies represented contrasting cultures. Illustrative of these cultural differences, some companies desired to condition their research funding on use of their own standard process for the conduct of in-house company R&D. They desired a detailed research plan and schedule. Frequent progress reviews by company personnel were proposed with each stage of the research being incrementally funded. Incremental funding was to be accompanied by unilateral termination options for the sponsoring company based not only on its evaluation of research progress, but also allowing termination because of changed company objectives or priorities, shortage of R&D budget, or any other reasons. Such an approach was not appealing to the university and its investigators, for it lacked the characteristics to which they were accustomed, i.e., freedom for investigators, non-intervention by sponsors during the course of the research, stable funding for reasonable periods of time, and above all, a mutual trust and confidence by sponsor and investigator.

Another example of initial relationship troubles occurred especially in research involving the development of new compositions of matter. The nature of the problem was such that it also appeared in the early days of company sponsored biotechnology research. To illustrate, when a university investigator produces a new and useful chemical compound, such as a new pharmaceutical compound which has a specific desired activity, the investigator has produced a significant end result which will probably be patentable. While the investigator may thereafter consider the exploration of all analogs of his or her compound to be routine and of little research interest, the company sponsor is compelled to make such an exhaustive exploration so as to establish the most secure commercial position. In these circumstances, any analogs discovered by the company, including the analog patents, belong to the company and it has no obligation to the university or its investigator for such analogs. By this process the original discovery can become essentially valueless commercially and the company thereby avoids any future royalty obligation even though the university investigator provided the "directions to the gold mine." A similar situation has occurred with company cell line derivatives made from university cell lines.

In earlier days of university-industry research relations, the matter of secrecy often was of significant concern. Companies live in a highly competitive commercial world where research is done in private and the protection of trade secrets is considered essential for success, if not survival. Industry did not relish the idea of sponsoring research in the completely open environment of a university, where its competitors had equal access and the results of research it sponsored would probably be published for all to know. The university was equally concerned that preservation of the unrestricted flow of information, through publication, scientific meetings, and open discussions, was essential to the continued expansion of knowledge. Fortunately, both parties soon came to realize that the commercial value of discoveries can often be preserved by patenting without the need for maintaining them in secret. Furthermore, while the "know-how" of commercial value which emerges from research may not be protectable under law, it is not effectively disseminated to commercial competitors, thereby allowing the sponsoring company to gain the advantage of market lead time. So, again industry found that a reasonable departure from their normal in-house practices did not necessarily lead to loss of the value of the university's research results.

In the process of resolving potential problems, universities and firms have developed the following set of guidelines, now applied fairly consistently nationwide:

1. **Research Selection**: Companies and universities seek to match their separate research interests.
2. **Direction and Control**: Direction and control is left with the faculty investigator, but with periodic progress reports to the sponsor.
3. **Diversion**: There is no evidence whatsoever of a shift in the balance between basic and applied university research.
4. **Quality**: There is no evidence that company sponsored university research is of lesser quality than peer reviewed research.
5. **Secrecy**: Free discussion of research results has been respected, with advance review by sponsors and brief delays in publication accepted for the sole purpose of permitting the timely filing of patent applications.
6. **Company Competition**: Respect for faculty and graduate student rights and prerogatives has become the standard for company R&D personnel.

7. **Ownership of Technology**: University ownership has become prevalent, but with an option to the sponsor for an exclusive, royalty bearing license covering commercialization. Costs of patenting and enforcement are borne by the company. Matters of analogs and derivatives remain subject to negotiation on a case by case basis.
8. **Confidentiality Protection**: Generally, the university is not obligated to protect company proprietary information revealed to its faculty since it has no internal security system nor adequate control of faculty actions. The company will safeguard unpublished university research results and plans.
9. **Faculty Conflicts of Interest**: Generally, the university cannot adequately control faculty activities, but requires disclosure and official review and counsels faculty on the need to avoid such conflicts.
10. **Full Cost Reimbursement**: Generally, companies will pay full direct and indirect costs.

There appears to be no question that companies have found university concerns to be sincere and meritorious. Although often in a radical departure from commercial practice, companies have been quite willing to work with universities to forge mutually acceptable research alliances protective of academic values.

To foster widespread awareness in the academic community of potential problems and the means for their resolution, conferences were held at Pajaro Dunes and later at the University of Pennsylvania. A Congressional committee also conducted public hearings to explore potential threats stemming from university relations with industry. In addition, both the academic and popular press have examined many aspects of university-industry research relations and offered opinions ranging from approval of the way problems were being resolved to pessimistic speculation about future disastrous consequences. Wide dissemination of the results of these conferences and hearings has made universities nationwide aware of the issues involved and informed about how they are being handled by others.

It is less clear how industrial firms came so rapidly to accept the universities' need to protect academic values while negotiating research agreements. Many industrial officials participated in the public conferences which had aired university concerns. While obviously trying to educate the academic community to the realities of the competitive marketplace, they also demonstrated a sincere respect for academic traditions and a cooperative attitude toward resolution of contested issues. Consequently, the potential for adversarial relationships gave way to the reality of a negotiating process characterized by brevity and good faith.

Adapting to Change: Assessing University-Industry Efforts

The adoption of negotiating guidelines, as outlined above, has removed a potential barrier to university-industry cooperation and provided a foundation upon which a long-term cooperative relationship can be built. To realize their full potential, however, university-industry research agreements must be mutually beneficial and also harmonious, based on trust and confidence.

For faculty and administrators at Washington University this is the most important lesson we have learned from our relations with industry. The concepts which have come to guide our research arrangements with industry represent a major departure from those which defined our relationships in the past with government agencies, foundations,

and other non-commercial sponsors. Among these new guiding concepts are the following:

- There should be a mutual understanding between the parties and respect for each other's interests.
- In exploring possible research relationships, the parties should objectively search for a convergence of interests. This is not to say that their reasons for pursuing common or complementary interests are necessarily the same.
- In structuring a cooperative research relationship, the parties should avoid ambiguity in defining essential responsibilities and expectations.
- There should be active and responsive participation by both parties whereby each contributes according to its resources and strengths, whether in technical or administrative areas. Each should bring significant contributions to the table.
- The parties should actively work to achieve mutual trust and confidence on a personal basis in all functions and at all levels of interaction. The relationship should be collaborative with open, two-way communications on all matters.
- Each party should be willing to provide reasonable assistance and support to activities by the other party within the broadest definition of the research collaboration.
- There is a need for shared and consultative decision-making on certain issues if the objectives of both parties are to be achieved. It follows that the parties must also be able to deal with and resolve disagreements.
- There should be a serious commitment by both parties to making the relationship work. The aim should be the development of a lasting relationship rather than exclusive attention to immediate, short-term results.

Thus, in working out mutually acceptable solutions to basic problems arising from research collaborations, universities are adapting quite well to the challenges of their new role as a creative resource in the service of society, without compromising the values inherent in their more traditional roles. There remain, of course, problems still to be solved, but they are relatively small and relate mainly to the rules for regulating internal conflicts of interest and commitment within academia.

In all likelihood, academic institutions will be as successful in resolving such problems of proper faculty conduct as they have been in protecting academic freedom and institutional autonomy from the purported threats posed by industrial research sponsorship. Notwithstanding the fears and suspicions which have been expressed, faculty members can reasonably be expected to understand and accept the need for self restraint and for adherence to explicit policy guidelines designed to preserve and protect the fragile fabric of academic traditions.

Influenced by the public, government, industry, and the nature of scientific advances, academic institutions have committed themselves to a more active and direct role in society and the economy. Research universities and their scientists have willingly and enthusiastically taken on new interests and activities. Prominent among these are extensive research relationships with industry in biotechnology and other fields, for only through an alliance with industry can universities fully deliver the benefits of their research to society.

Bridging the Gap Between Academia and Industry: The Scientist's Role

Jeffrey S. Price
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Scientific collaborations between academia and industry have existed for many decades in this country. From the very beginning, these collaborations have been accompanied by concerns among some members of academia – more concern, I think, among those less familiar with the phenomenon than among those participating in it or giving it careful study. I shall not attempt to raise or answer all those questions that have been debated for the more than ten years since the emergence of the "new biotechnology industry" – an industry which is perhaps less accurately described as new than as having been revitalized by the application of fundamental research discoveries, primarily in the areas of biochemistry, microbiology, cellular immunology, and molecular biology.

Instead, I shall attempt to describe, from the perspective of someone responsible for managing science and technology in one of the largest of the biotechnology companies, what biotechnology firms are trying to accomplish, why research scientists want to be involved in the effort, what these firms want and need from academia, the mutual benefits that result from academia-industry collaboration, ways to insure a high frequency of success for such collaborations, and some of the problems that will very likely require continued attention in the years to come.

Why Do Science at a Biotech Company?

Beginning in the early 1970's and increasing at a steady rate down to the present, small companies have been formed to apply the results of over twenty-five years of research in genetics, biochemistry, and molecular biology. These companies arose and grew from the vision and commitment of their founders, the speculative faith of their initial venture partners (and later, thousands of shareholders) in the future success of the technology, and the creativity and productivity of the scientists, including physicians and engineers, who were willing to take career risks to participate in an opportunity they believed to be unique. What are some of the factors that motivated scientists to join in the work of these firms?

The migration of scientists from academia to industry is certainly not unique to biotechnology. Industrial firms have been providing careers for chemists and engineers throughout this century. The phenomenon is not even novel in the life sciences. Pharmaceutical companies have attracted biochemists, microbiologists, physiologists, and physicians for several decades. What is unique is the large number of molecular biologists and biochemists who have come from academia in the past ten years, not with the purpose of entering an established industry, but in order to participate in the creation of a new industry based on the fundamental and applied research they had been previously performing in academia. It is important to realize that what is called the "biotech" industry has attracted some of the brightest young scientists to emerge from these fields

in this decade, and their impact on the behavior and expectations of industrial scientists is likely to be profound.

One of the primary attractions has been the potential opportunity to discover and develop new approaches which can be directly applied to improving human health care. Probably seventy-five percent of the research of the major biotech companies is aimed at developing therapeutic, diagnostic, or prophylactic products for physicians. A similar motivation – the desire to see practical and beneficial consequences from the understanding of science and the development of technology – is shared by many physicians who combine research with clinical practice.

Development of one of these new products, a natural immune-system regulator called Interleukin-2, can be cited as an example of how such hopes have been realized. Pure pharmaceutical grade IL-2 was made available to treat cancer patients less than a year from the time the human gene had first been inserted into bacteria. The team of industrial scientists who developed the product immediately began close collaborations with clinicians, of whom Dr. Steven Rosenberg, Chief of Surgery of the National Cancer Institute was one among many, in order to learn how to use this human protein to treat cancer in patients whose immune systems appeared no longer able to protect them. In addition to publishing rapidly their own research with this human protein, they immediately began to supply the pure protein to hundreds of scientists throughout the world. As a result, thousands of scientists have experimented to date with a substance previously available, only after tremendous labor, in trace amounts and crude preparations.

Before the application of genetic engineering, forty liters of cell culture were required to obtain a 10% pure preparation containing at most a few micrograms of IL-2, scarcely enough to treat a single mouse. In those days significant biomedical research with this substance was extremely difficult. Today, hundreds of thousands of vials a year, each containing several milligrams of pure protein, are being provided without charge for basic as well as clinical research. Activities similar to those with IL-2 have been repeated at Cetus and other companies with many other protein regulators of the immune system. The result has been an exponential increase in basic research leading to an unprecedented accumulation of understanding of the functions and operation of the human immune system. This is no small achievement since the human immune system may be described as a single extremely complex organ of the body – its complexity rivaling that of the brain.

The internal structure of the new biotechnology companies is, as a rule, designed to encourage and support collaboration among scientists of diverse disciplines to a greater degree than is routinely found in universities. Such scientists are attracted to a system in which resources are pooled, where a full range of talents is available, where molecular biologists, fermentation engineers, pharmacologists, and clinicians are working together on fundamental and applied research, where there is a strong commitment to getting things done rapidly and with a minimum of bureaucratic delay, and where an individual can be involved in a project all the way from conception to application to human disease and the increased understanding of biological mechanisms.

In addition to the above, there is also a commitment to publication as great as in academia. If rapid publication of research were not strongly encouraged, the new biotech companies would certainly be unable to attract and retain the bright scientists and engineers they now possess and will continue to need. The strong commitment to dissemination of research results, generated and maintained by the scientists themselves, is what

may make the environment for fundamental research in biotechnology firms unique in American industry.

Scientists in the biotechnology industry share many of the same values and goals which motivate university scientists. Their relationship is or should be mutually supportive and beneficial. For example, Cetus, a company of 700 people, maintains a scientific group of about 450, including 130 Ph.D.'s and M.D.'s, and double that number of staff with masters and bachelors degrees in science and engineering. In what follows, I will attempt to list the kinds of things scientists in Cetus expect from their colleagues in academic and government laboratories. It is likely that the expectations of scientists throughout the biotechnology industry are similar.

What a Biotech Company Expects from Academia

We (at Cetus) expect that university and government scientists will focus primarily on fundamental research designed to elucidate the basic mechanisms of living systems. In particular, we are extremely interested in understanding such things as the regulation of cell growth, differentiation, and the development of organs and organ systems; the control of gene expression; mechanisms of pathogenesis; the relationship of protein structure to function; and fundamental principles of process design and engineering. We are intensely interested in but cannot afford to devote a great deal of our resources to these areas. We can contribute materials and technology, such as recombinant genes, proteins, and cloning vectors, and, from time to time, we can help by purifying and sequencing a gene or protein or by synthesizing peptides or oligonucleotides. We can also provide facilities for testing a process and contribute some financial support. We expect that scientists in academia and government will rapidly disseminate their results and speculations, and we certainly count ourselves among the population of scientists with the commitment to evaluate, contribute to, and benefit from those results.

We also expect to find a continuing stream of bright, productive people emerging from these institutions, with and without advanced degrees, who have a clear understanding of the fundamentals of science, some specific training, and a potential interest in joining our staff to engage in a combination of basic and applied research.

In the case of Cetus, all research was initially performed in-house. For several years academic contracts were limited to consultation. Today we look for collaborations with academic and government scientists that emerge spontaneously and that are based primarily on the scientific judgments of the scientists themselves rather than on business relationships between Cetus and the universities or the government. Such collaborations routinely entail exchanges of materials, technology, and, of course, research results and their interpretation. In such collaborations we expect joint publication and scientific credit according to the same generally recognized standards practiced in academia for determining authorship.

In addition, Cetus and other biotech companies exchange scientists and postdoctoral fellows with universities, providing our scientists with the equivalent of sabbatical programs. Many predoctoral students have completed their thesis research in industry laboratories. Numerous company scientists and physicians maintain adjunct scientific and clinical appointments in universities, teaching courses and seeing patients without remuneration. We also welcome the opportunity to seek consultation from our academic colleagues in order to obtain independent views on the soundness of various research strategies or to discuss potential approaches to therapy for specific diseases. These consulting relationships are primarily non-exclusive and often non-confidential. We com-

pensate our colleagues for their time and effort as appropriate. Where specific details of yet-to-be published research are discussed and we have not yet filed appropriate patent applications, we may ask that the consultation be confidential until those results are published.

We desire the opportunity to commercialize inventions in our fields of interest made either in academia alone or jointly with scientists from biotech firms. For most proprietary processes it is sufficient that commercial licenses be non-exclusive. For some products, notably therapeutics, it is necessary to request exclusive licenses, in part because of the high subsequent costs to develop these products. Today, a typical human therapeutic protein will cost from $50 million to $100 million to develop to the point of registration for sale. Unless a company's share of the potential market for a product is substantial—which will be much less likely if the product is generic and produced and sold by many companies—the company will not be able to recover its research and development costs for that product. It must also recover costs for the products that fail to make it from research, development, and clinical testing to registration and marketing.

Biotechnology companies also sponsor a limited number of research contracts in which both the laboratory and the university of the collaborating scientist receive direct financial assistance. These cases generally emerge from collaborations originating between scientists in which it appears that results will continue to be of mutual interest and may eventually lead to either valuable new technologies or products with commercial potential.

What One Biotech Company Contributes

What do we at Cetus do to help insure that what we expect from academia continues to be realized? There is nothing magical here. We have limited resources, so we can only make limited contributions. Today, our product sales are not more than $10 million/year. Yet, we spend over $40 million/year on research and development, an amount a pharmaceutical company with about $500 million/year in sales might be expected to spend. Obviously, we have every expectation that this ratio will be reversed in the near future. Ultimately, the goal for our industry is to attain a level of research and development spending similar to that of the pharmaceutical industry, i.e., 10-15% of sales.

Here is a list of what one company does to help. Cetus spends hundreds of thousands of dollars a year to support scientific meetings throughout the world. We donate tens of thousands of dollars to what we feel are useful seminar series at local universities. We occasionally donate to industrial affiliates programs in university research departments which appear to have good potential. We provide additional income to more than fifty university consultants and fund ongoing research collaborations with at least ten university laboratories. We hold in our own laboratories frequent symposia open to the scientific community on a wide range of scientific topics. We support clinical research in over fifty institutions by supplying potential therapeutic products and scientific expertise, and also by covering part of patient costs. At the National Institutes of Health and the National Cancer Institute, and for human clinical trials sponsored by the NCI, we supply the human proteins and all of the information we can collect on the biochemical and biological behavior of these proteins.

The total expended in all such activities typically approaches ten percent of our annual R&D budget. This is surely a significant contribution in proportion to our size and resources. In the future, as our resources grow through sales of successful products, we

will be able to contribute more. In addition, as already mentioned, Cetus, like other biotech companies, supplies large quantities of rare human proteins as well as proprietary technology for fundamental biological and clinical research. Such reagents are extremely expensive when generated at noncommercial scale, and the cost of developing the technology is at least as great as in academia.

Here is an example of a recent biotechnology invention which is having a dramatic effect on academic and government research. In the past two years, scientists at Cetus have developed a technique for rapidly amplifying any specific DNA or RNA sequence of interest over a millionfold in crude or pure DNA (or RNA) preparations. The inventors call this technique the "polymerase chain reaction." This DNA amplification method makes it possible to detect the AIDS virus, HIV, directly in samples of human blood even if the virus is hidden away in only one of every 10 million blood cells. This ratio may be typical in infected patients. But perhaps the most important impact of the technique is the ability to clone these specific amplified DNA sequences directly into a bacteriophage vector for rapid sequencing and further engineering. This means that a small research laboratory searching for genomic determinants of genetic disease can now sequence many more stretches of the human genome than heretofore, and in a fraction of the time previously required .

We have also built, originally for our own use, an instrument that automates the technique. We have made the technique widely available, not only through the scientific literature, but also by training scientists in Cetus laboratories. The technology and the instruments are being provided to selected collaborators in academic and government labs, including the Centers for Disease Control in Atlanta, the FBI, and the Pasteur Institute. The range of applications, from gene synthesis and sequencing to detection of known and novel pathogenic organisms, determination of genetic disease susceptibility, detection of cancer, and forensic medicine, is quite wide. Working with Perkin-Elmer, a venture partner with a large research instrumentation business, we have plans to build and market an instrument using this technology.

The development of this technique has parallels in academia. The pH meter and high speed analytical and preparative centrifugation techniques, ideas initially conceived and developed in the academic laboratories of the California Institute of Technology, were ultimately manufactured and marketed by Beckman Instruments. Later, DNA and protein sequencers and synthesizers, originally designed and developed in the laboratory of Leroy Hood at Cal Tech, were ultimately manufactured and marketed by Applied Biosystems. The technologies created by scientists at Cal Tech have had an enormous impact upon biomedical research. We think DNA amplification technology will have a similar impact. It is important to note in this context that, through the combined efforts of scientists in academia and industry, it has become possible to make such technologies broadly and rapidly available for research virtually as they are being developed. Scientists now have a chance to participate in the design of the technology they will need.

Mutual Benefits

I will now summarize what I believe are mutual benefits that have flowed from collaboration between academia and biotech companies during the 1980's. First, corporate scientists benefit from research results that provide insights into basic mechanisms of life processes. Most, but not all of these results are obtained in academic or government labs. Increasingly, corporate laboratories have also been playing an important role. However, applied biotechnology has generated a rapidly growing demand for even more

basic research. Biotech firms can develop and provide novel pure human proteins much more rapidly than existing academic laboratories can study and understand the scope of their biological function. Academic scientists can now obtain rapid technological help and a ready supply of otherwise scarce critical biological or biochemical reagents for basic research use. They no longer need to spend limited time and funds producing such reagents or developing processes for supply. It would be highly impractical to develop most critical reagents and related technology in academia, due to the quantities and types of the human, equipment, and financial resources required. Production of materials is, in any case, not a major responsibility of academia.

The research results, both fundamental and applied, which are generated by such collaborations are generally disseminated publicly, thus benefiting not just the participants but all other interested scientists. I can testify from twelve years of experience at Cetus Corporation that the myth of trade secrets is just that – a myth. Nearly everything we discover is published rapidly. The requirements of the patenting process may delay results from 30 days to, on occasion, a maximum of several months. This is within the range of time required for the scientific publication process itself.

It is not fundamental research discoveries, but rather certain commercial process steps, which are kept indefinitely as trade secrets. These secrets are maintained at the substantial risk that a competitor may obtain a patent on these steps and thereby be able to block their use by the firm which developed them. A second myth, which proclaims that people in academia are devoted exclusively to knowledge for its own sake, is countered by the fact that academics share the competitive drives and opportunities of the general population. Few scientists, whether academic or industrial, want to work in a backwater or have their work go unrecognized. Achieving priority in research is as important to scientific teams as to individuals, and collaboration with corporate as well as academic colleagues often provides a competitive edge.

Many of the new biotech companies serve in some respects as half-way houses. Most were originally more academic than commercial in character. Although the most successful companies have necessarily developed strong business management and sound business strategies, the deep academic roots of the scientists who staff these companies have helped to maintain and strengthen the scientific component of their direction and management. If bright, inventive, and highly productive scientists are to be attracted and retained, they must be provided with the opportunity to do fundamental research and to communicate and collaborate with their colleagues.

The existence of an arena for collaboration between strong and productive corporate and academic research organizations provides an excellent opportunity for individual scientists, physicians, and engineers to create a working environment which suits their own research needs and scientific focus, whether fundamental or applied. Those who are so inclined can find increasing opportunities to spend time in both worlds, sequentially or even simultaneously. Moreover, good collaborative research and increasing job mobility between the industrial and academic sectors effectively enlarge the overall career opportunities for all scientists. A form of buffer is thereby provided against economic changes which may serve to shrink or enlarge the availability of jobs or research funds in either sector.

I personally believe that the often cited risks of collaboration are dwarfed by the magnitude and scope of existing and potential benefits. In general, corporate research organizations simply do not seek to contract significant amounts of applied research to academic laboratories. Nor do they intend for academic scientists to manage corporate research, in conflict with their own academic commitments. The best collaborations are

those which bring together complementary skills and resources. Such collaborations, when successful, result in joint rewards. When such rewards are not allocated fairly, the result will be a chilling effect on the frequency of future collaborations.

Problems with Collaborations—Real and Imagined

It would be naive to expect the absence of problems in corporate-academic collaborations. Most of the problems which have developed in biotechnology, however, are not unique to this field but are instead similar to those to be found in any sort of intense collaborative scientific activity, whether within or between corporate and academic research organizations. The greater the extent of the collaboration, the higher the probability that problems like communications breakdowns will occur. These are the risks associated with the benefits of collaboration. The number of such potential conflicts can be greatly reduced by open, early, and continuous discussion among collaborators.

The potential negative effects of biotechnology on the environment or on human health is another problem area where concerns have been frequently raised. Once again, such questions are by no means unique to academic-corporate collaboration in biotechnology, but are instead relevant to the conduct of scientific research in a wide range of fields throughout the world. There is no reason to doubt that corporate scientists are as concerned as academic scientists about their physical environment. Neither can it be argued that academia possesses a monopoly on concern for human health. In fact, as mentioned above, many biotech companies are devoting the bulk of their efforts and their resources to solving problems in human health care. It would be ludicrous to claim that these same scientists would show special disregard for the potential negative effects of their research on human health.

In reality, a different and perhaps even greater responsibility is assumed by corporate scientists who are working to develop products to be used by society—their own personal responsibility for the quality and safety of such products. Thus, corporate biotechnology research laboratories in this country can be expected to be at least as scrupulous as academic laboratories with respect to the potential societal effects of their research work, for they have so much more to lose financially if environmental accidents or bad judgments reduce their value in the eyes of the financial community.

Many biotech companies are attempting to improve the understanding of the academic community and the general public about the nature and activities of the biotech industry through individual lectures to high school, college, and university audiences, through collaborative research with universities, and through industrial associations. Clearly, much remains to be done, since misunderstanding remains. For example, a problem that I find particularly distasteful, though fortunately it occurs infrequently, is the tendency for some academic administrations to treat corporate scientists as second-class citizens, not entitled to the same degree of openness and collaborative opportunity as scientists from the academic institutions. On occasion, this takes the form of the expectation of cash in advance before any scientific exchange can take place. Fortunately, most scientists in academia will not tolerate this approach.

Another problem, more serious for the future than it actually is at present, may be the approach of tying up entire academic research departments with corporate sponsorship. Individual scientists in those departments may then be forced to collaborate only with scientists of a single company, since no rival corporation would be able to commer-

cialize the results of the collaborations. We continue to collaborate with some scientists in such departments, but the long-term effect may be to discourage broad collaboration.

Some university administrators have held that all liabilities for collaborations should rest with the corporate side, and they have therefore asked for broad indemnification. Usually, however, we find we can reach agreements which provide that each organization will accept responsibility for its own acts.

The generation of research contracts and license agreements is an evolving area, where the potential for conflict once seemed high, but where the rate of actual conflict is continually declining. It should not be surprising that past conflict were largely due to lack of experience among administrators in some institutions and in some companies. They were led to have unrealistic expectations about the magnitude of the potential reward. I can state from my own experience that we have reached satisfactory agreement in nearly all of the many cases we have negotiated.

The Future

I am confident that as the biotechnology industry continues to grow and the successful companies mature, more, not less, collaboration with academic and government laboratories will take place. The trend toward an increasing rate of exchange between academic and corporate research staffs will and should continue. It will be incumbent upon academic scientists and institutions to make more of an effort in the future to communicate with the public in order to increase public understanding of the social relevance and importance of their work. For their part, corporate scientists and their corporate management must be more active in urging government to allocate to academic biotechnology research a bigger piece of the funding pie. Though some of us in the corporate world have offered help, the response from academic institutions has been quite limited to date.

Finally, corporate-academic collaborations can have key strategic value for the country. The dissemination of the results of biotechnology research, with rare exceptions, must be considered to be international. Thus, when one nation increases funding for basic research, scientists in all countries ultimately benefit. One way by which our nation can remain competitive in the development and application of biotechnology to commerce is by encouraging the kind of collaboration between corporate and academic scientists which will most likely lead to the rapid local commercialization of discoveries. We would thereby facilitate the preservation of our proprietary position at home. This may provide the kind of competitive edge we need.

Reflections of an Industry-Supported University Scientist

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This paper will present one scientist's view of university-industry relationships and describe how a successful relationship can lead to rapid research advances through collaboration and interaction. It will also describe some potential problems and pitfalls that should be avoided. The examples and lessons are drawn from my experiences as a faculty member at Washington University engaged in establishing and bringing to fruition a strong collaboration with the Monsanto Company in the field of plant biotechnology. In many respects this collaboration has been ideal and the reader is cautioned not to conclude that all interactions will be as positive as the one described here. However, it is hoped this case may serve as a model for establishing and maintaining long-term research relationships between groups of scientific colleagues in institutions whose goals are different, but whose scientific approaches can be parallel or convergent.

Establishing a Good Interaction

After joining Washington University in 1978, I embarked on research projects based in large part on post-doctoral experience in molecular biology and along the lines of what I believed to be good research practice. Throughout my training a major interest had been the application of basic research to the needs of agriculture, both in plant improvement and crop protection. However, potential applications of molecular biology to agriculture did not begin to appear until the early 1980's when it became evident that transformation and regeneration of plant cells into whole plants would soon make it feasible to transfer target genes into plants. With this development came the conviction that molecular biologists might be able to contribute to plant production and their protection against plant pests and diseases.

In the early 1980's, the Monsanto Company established a research group in plant molecular biology, interacting in large part with a Washington University colleague, Professor Mary-Dell Chilton. That collaboration was a successful one, but was dissolved in 1983 when Dr. Chilton left the University to join the Ciba-Geigy Research Group in North Carolina. In those early years my research was watched and encouraged by the group at Monsanto, but was not funded by them. In 1981, I submitted a proposal to Monsanto Company seeking research support. After about a year of review, it was decided that the proposed research was interesting and had a chance of success, although it was still difficult to determine whether the research would have useful field applications. With this funding, a graduate student and a post-doctoral associate began work on a project that ultimately led to generating transgenic (i.e., genetically engineered) plants resistant to virus infection (Abel et al., 1986).

For the first several years the research was conducted largely in my laboratory. However, the Monsanto research group members, under the direction of Dr. Robert T. Fraley, were intellectual and technical collaborators and provided tools that made the

research proceed more expeditiously. Dr. Fraley and I met frequently to brainstorm ways in which the research techniques might be improved. As the target genes were being constructed for insertion into transgenic plants, it became obvious that appropriate vectors for delivering the gene would be required. Two kinds of vectors were needed, the first to ensure the high level expression of a (viral) gene in transgenic plants, and the second a bacterial strain to deliver the gene into the plant chromosome. Strains to deliver the new gene were developed in pioneering work by Dr. Chilton here at Washington University, complemented by researchers at the Max-Planck Institute in Cologne, West Germany, and the research group at the Monsanto Company (Barton et al., 1983; Zambryski et al., 1983; Fraley et al., 1985).

The task of constructing intermediate plasmids to carry the target genes into transgenic plants was assumed by the teams of Dr. Fraley and Dr. Steven G. Rogers at the Monsanto Company. It is important to note in this context that the Monsanto research group was strengthened by the hiring of university-trained, highly competitive research scientists interested in plant molecular biology and genetic engineering. Fraley and Rogers quickly recognized that my work would be limited without access to some of their vectors and they chose to make them available as soon as they were sufficiently developed. One plasmid enabled us to proceed with construction of the chimeric gene. Since the second plasmid was more experimental at that point, the chimeric gene was prepared at the Monsanto Company. Further characterization of the chimeric gene and its introduction in the *Agrobacterium* cells were done in both laboratories.

Concurrent with the development of methods for causing high level expression of foreign genes, Dr. Robert Horsch and his colleagues at Monsanto were developing techniques for rapid and convenient transformation and regeneration of plants using relatively simple techniques. Dr. Horsch offered to apply these techniques to the transformation and regeneration of the first set of plants with the chimeric genes which we had produced. Again, we had access to very important technology prior to its general availability to other research laboratories. Cooperation between post-doctoral associates and graduate students in my laboratory and the research group at Monsanto led ultimately to the production of transgenic plants that contained chimeric genes, including those that encoded viral sequences. These transgenic plants were brought back to Washington University for full molecular characterization and an examination for altered phenotypes which might have been caused by the expression of the foreign gene. As a result of these experiments, we were pleased to discover that transgenic plants expressing the viral capsid protein gene of tobacco mosaic virus were resistant to infection by TMV. These first results were documented repeatedly with plants derived both at Monsanto and at Washington University, and led to a joint publication which recognized the role of researchers at both institutions (Abel et al., 1986).

The Second Phase of the Interaction

Once it became apparent that our approach would produce protection against tobacco mosaic virus, Monsanto expanded their research capabilities in order to demonstrate that similar technical approaches could be used to derive resistance against other plant viruses. Through their own scientific expertise and the assistance of outside collaborators, primarily Professor Nam-Hai Chua at Rockefeller University, they were able to demonstrate successfully in a relatively short time that resistance against three other viruses could be provided (Tumer et al., 1987; Cuozzo et al., 1988; Hemenway et al., 1988). I served as a consultant and advisor to Monsanto Company in this research initiative.

During this same period, another Monsanto research scientist, Dr. Sheila McCormick, was cooperating with researchers at Washington University in an effort to generate transgenic tomato plants expressing the TMV capsid protein gene. Once produced, these transgenic tomato plants were brought back to Washington University for further study. The joint efforts of my research group at Washington University and the research group at Monsanto Company, in cooperation with a research group headed by Professor Nam-Hai Chua, led to the demonstration that resistance could be achieved against four different types of viruses in transgenic tobacco and tomato plants. The fact that the first phase of research on TMV resistance ran from 1981 to 1985 and the second phase from 1984 to 1987 clearly demonstrates that rapid progress is possible when groups of scientists in industry and academia share common goals and interact extensively.

Interaction Between Members of the Research Teams

During the early years of the collaboration, both research groups accepted each other's distinct roles and recognized that their different areas of expertise were in fact complementary. This appreciation made possible the open sharing of information and protocols, accomplished by frequent telephone calls and visits between laboratories. Active interaction took place at all levels, including research technicians, graduate students, post-doctoral associates, and research leaders.

The information shared was, by and large, as open as could be expected given Monsanto Company's need to maintain a certain amount of proprietary information. This issue of proprietary limitations on information flow was anticipated. However, in the beginning, Monsanto's need to withhold proprietary information was more difficult for graduate students and post-docs to accept than it was for me. But as cooperation proceeded and information was shared on an increasingly regular basis, the issue of proprietary information diminished in importance. By the time the first jointly-authored papers were published, with acknowledgement of the effort of both research groups, it had largely dissipated.

The research group at Washington University proceeded toward goals which were different from those of the Monsanto group. Whereas our interests were primarily to derive an understanding of the cellular and molecular basis of the engineered trait, the Monsanto Company group had necessarily to be interested in demonstrating the extent to which commercial opportunities could be protected and advanced. Nevertheless, the group at Washington University maintained an interest in demonstrating the efficacy of the disease resistance trait under glasshouse and field situations.

The most recent example of cooperative interaction between the two groups came during the summer of 1987 in a successful field trial of the genetically engineered plants. Application for permits to conduct the experimental test, the establishment of the agricultural setting, and the management of the farm itself were all undertaken by Monsanto scientists and managers. The role of the university scientists was to evaluate the disease resistance trait. The test was conducted in close interaction among members of the two groups, and has led to lecture presentations and manuscripts recognizing the contribution of each research organization (Nelson et al., 1988). The two research groups agreed to meet throughout the process on a periodic basis, to share unpublished data, and critique the research plans and ideas of all the members. The goal was not only to exchange information useful to other members of the project but to produce a greater appreciation of the individuality of each scientist. The effort was, by and large, success-

ful, leading to a better general understanding of each person's capabilities and needs and of the problems encountered.

One important difference between the two groups is in the degree of training and expertise. Whereas the university group is largely made up of graduate students and postdoctoral associates, the Monsanto group is dominated by well-trained professionals whose technical proficiency is somewhat higher than that of some of the students or postdocs. This difference has caused some problems, but a serious split has been avoided through the efforts of the group leaders and the scientists themselves. The belief that a set of experiments might be done more efficiently by an individual other than the trainee to whom it was given has occasionally led to a sense of frustration on the part of the research directors. On the other hand, there is the potential for scientists at Monsanto to envy what they regard as the greater freedom of university scientists to undertake "chancy," but potentially more exciting experiments.

To avoid such problems it is important that the research directors keep clearly in mind the distinct role of each research group, indeed, of each individual researcher in the program. There is always the possibility that such fierce competition may arise between ambitious members of the two groups that the friendship and trust upon which successful collaboration is based will be destroyed. To prevent this, it is essential that periodic group meetings address issues of mutual concern. Furthermore, open disclosure of goals by research leaders is required to ensure that research projects are complementary and not competitive. Repetition of one group's experiment by another should be encouraged, but establishing long-term research goals which directly overlap with each other must be avoided because of the risk that ill will may arise and eventually destroy the collaboration.

An essential element of any successful collaboration is that every scientist take care to give ample credit to others during the preparation of manuscripts reporting jointly derived research results. This task might appear somewhat more bothersome to members of the academic community than to those in industry laboratories. A graduate student whose thesis project includes research results to which scientists from industry contributed must give proper credit during the preparation and presentation of the thesis. It has been our belief that technical and intellectual support contributing to the formulation and successful testing of hypotheses or the framing and answering of research questions are critically important parts of any thesis project and must therefore be acknowledged in theses, as in other publications. It is the responsibility of the thesis advisor to ensure that other parts of the thesis clearly demonstrate the student's unique skills and the specific contributions made by the student to the collaborative project. Consequently, theses presented by graduate students who were part of the groups included both joint and independent research. The burgeoning field of biotechnology thrives on interaction and collaboration, and rapid advances can best be made through such arrangements.

The issue of publication delay has the potential to be a major roadblock to successful collaboration. There are numerous examples in the record of university-industry interactions of extensive review and clearance procedures for industry-funded research prior to submission for publication. To avoid delays that might cause harm to the career of the young scientist, we have found the constant communication and sharing of information to be essential For example, by the time a series of experiments has led to a conclusion that should be published, this information has already been conveyed informally by the research directors and has been scrutinized by the collaborators. It is readily ap-

parent from such examination and evaluation which data should be prepared for publication and which should not.

When information is jointly shared, manuscript reviews are able to proceed rapidly since each research group has received the data well in advance. Likewise, that information which should be protected by patent application is apparent well before final data are gathered, and appropriate action can thus be taken as the research results become final. It is this process of open and frank disclosure and discussion that enables timely action to be taken jointly without controversy, whether in reviewing manuscripts for publication or preparing conference presentations.

Conclusions

In sum, the interaction between my research group at Washington University and the research group at Monsanto Company has been open and interactive from its inception. Careful recognition of each person's contribution to the program, whether it be in the University or at Monsanto, is essential to the well-being of the long-term project. This is facilitated through frequent interpersonal communication and through recognition of the contributions of each member of the team, when appropriate, in publications and at conferences and seminars. To call this interaction anything but a true collaboration would be inaccurate. Certainly there are individuals in each group who contribute proportionately more to the progress of a given project. However, such persons have been supported intellectually and technically by the advances that others have made and these advances must be recognized. If the trust and friendly interactions disappear, scientific exchange and rapid progress will diminish accordingly. It is the role of each lab group leader to ensure that this unfortunate result is avoided by encouraging members of the different groups to share frequently and openly the results of their research.

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University Entrepreneurship and the Public Purpose

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Universities, like other complex institutions, adjust their goals and practices to changes in the broader political and economic environment within which they function. Over the past decade, a number of factors have been responsible for producing a closer coupling between academic and corporate institutions. The result has been a merging of corporate and university values for both the faculty and the institutions.

Some view this as a positive sign. They argue that faculty and curriculum can become stale, irrelevant, or outdated if they are too insulated from wordly affairs. Many advantages are cited in promoting closer ties between the academic and industrial sectors, not the least of which is opening up new funding sources to the university. It is also argued that the country as a whole benefits from university-industry partnerships because of improved technology transfer (Bearn, 1981). Too many useful inventions and discoveries remain unrealized because they are not brought to the attention of the innovation sector. According to former Presidential science advisor George Keyworth, unless universities and industry work more closely, the United States' industrial competitiveness will decline precipitously (Keyworth, 1982).

Universities have also begun to emulate the private sector by adopting management practices and efficiency criteria, by profiting from faculty discoveries and inventions, and in a few instances by direct investment in commercial ventures. Also, the concept of the "corporate liaison program," which allows universities to earn income by providing companies with privileged access to faculty research, has gained wide acceptance.

The distinction between universities and corporate institutions in mission, mode of operation, and public purpose has been widely recognized (Abelson, 1982). Bartlett Giamatti, when President of Yale University, highlighted the differences as follows: "the academic imperative [is] to seek knowledge objectively and to share it openly and freely; and the industrial imperative [is] to garner a profit, which creates the incentives to treat knowledge as private property" (Giamatti, 1982, p. 1279).

Cooperative agreements between the academic and business sectors can sometimes result in uneasy compromises. In the past several years there has been considerable debate about the proper boundaries for these contractual arrangements. The debate has been spurred by a new generation of financial and research partnerships, perhaps most visible in the area of biotechnology.

I shall argue that these linkages have created an entrepreneurial atmosphere that has begun to alter the ethos of science. Norms of behavior within the academic community are being modified to accommodate closer corporate ties. In addition, there are more subtle losses to society when the leading faculty in entire disciplines have financial interests in the commercialization of research.

To gain a better grasp of these changes, the paper will proceed as follows. First, I shall explore a metaphor that conceptualizes the university as an institution with multiple personalities in dynamic equilibrium. Second, I shall identify several factors external to the

university that are responsible for producing closer ties between academia and industry. Third, I shall sketch out three areas of potentially adverse consequences which follow. Finally, I shall examine one of these impacts, namely the long-term social consequences of the melding of corporate and academic cultures, by examining the case of biotechnology.

The University's Multiple Personalities

It is useful to think of the university as an institution with multiple personalities. Each personality symbolizes a distinct form of institutional identity with its own goals and responsibilities. Conflicts that arise over university-industry connections often reflect more deeply rooted tensions among these multiple forms of identity.[1]

- **Classical Form:** Knowledge is Virtue. In its classical personality, the university is viewed as a place where knowledge is pursued for its own sake. The problems of inquiry are internally driven and bound by the norms of university cooperation.
- **Baconian Ideal:** Knowledge is Productivity. The main function of the university is to provide personnel and intellectual resources for economic and industrial development. The pursuit of knowledge is not fully realized unless it can contribute to productivity. The responsibility of the scientist begins with discovery and ends with application.
- The **Defense Model:** Knowledge is Security. University laboratories and the scientists who manage them are viewed as critical resources for national defense. Universities differ in their willingness to undertake military research. Policies restricting classified or weapons research represent a barrier to the fulfillment of this model.
- The **Public Interest Model:** Knowledge is Human Welfare. According to this view, the role of the university is to solve major human health and welfare problems such as dread diseases and world hunger. Professors are viewed as a public resource called upon to tackle complex medical, social, economic, and technological problems.

The concept of multiple institutional personalities helps draw attention to the fragility of their interrelationships and the potential for conflict among the distinct values and responsibilities associated with them. The equilibrium in which these personalities coexist in universities is subject to change as a result of external forces. Recent interest in creating closer ties between the corporate and academic sectors reflects a greater emphasis on the Baconian identity, whereas the Defense Model is being aggressively promoted by those advocating the Strategic Defense Initiative (SDI). In both cases, external forces are contributing to a shifting balance in the academic culture, away from the classical and public interest models.

External Factors Promoting University-Industry Partnerships

The success of Japan's industrial economy has been explained in part by the country's efficiency in exploiting new technology for industrial purposes. Alternatively, the declining competitive position of the United States has been attributed to its failure to bring new technological ideas quickly enough into industrial application. George Keyworth, speaking as Presidential Science Advisor, noted that "most academic and federal scientists still operate in virtual isolation from the expertise of industry and from the ex-

perience and guidance of the marketplace" (Keyworth, 1983, p. 609). He attributed the separation of academia from industry as a "root cause" of the sluggishness of the economy.

In response to the challenge to improve innovation in American industry, both Congress and the Executive have supported policies designed to create closer collaboration between universities and the private sector. For example, new federal patent legislation, passed in 1980, gave universities and small businesses greater incentives to exploit faculty discoveries arising from federal grants by relaxing criteria for federal approval of licensing agreements between universities and private businesses. In the same year, a revision in the tax laws created the Research and Development Limited Partnerships (RDLP), a financial instrument for attracting R&D capital to university campuses. The RDLP structure provided for special tax shelters and high investment income. The Office of Productivity, Technology, and Innovation (OPTI), created in 1981, promoted the use of RDLPs at universities as a means of generating alternative sources of research capital and accelerating the transfer of federally funded technology. Finally, the Economic Recovery Tax Act of 1981 allowed a 25% tax credit for 65% of a firm's payments to universities to support basic research. The law also permitted a larger deduction for charitable contributions of equipment used in scientific research (Johnson, 1982).

The new structural forms for stimulating industry investment in university research were part of an overall plan for reindustrializing the U.S. economy. The strategy of "privatization" – put simply, less government and more private initiative – has been applied to every phase of American life from social programs to the government's own printing office (Smith, 1985). To achieve its goals, the Reagan administration sought lower taxes and presented Congress with reductions in most major domestic budget categories, including scientific research (defense-related research, in contrast, was increased). Anticipating reductions in research budgets and facing a more favorable environment for collaboration, universities moved easily into agreements with the private sector. Some of the largest financial collaborations took place in electronics and biotechnology (Norman, 1982; Zinder & Winn, 1984; Kenney, 1986).

Potential Negative Impacts

The potential adverse impacts of corporate-university collaborations can be divided into three general areas: those diluting the goals of science; those conflicting with the mission of the university; and those having deleterious societal outcomes.

A number of questions have been raised concerning the goals of science. When academic science draws more of its funding from the private sector will that skew the fundamental research objectives? Will scientists with entrepreneurial ties lean toward research programs with a greater commercial emphasis? The only study attempting to answer these questions was based on a survey of biomedical scientists. After questioning over 1200 faculty in 40 major universities in the U.S., Blumenthal and his colleagues concluded that "faculty... who were receiving industry support tended to publish more, patent more, earn more, serve in more administrative roles, and teach as much as faculty without industry funds" (Blumenthal et al., 1986b, p. 1364). They also found, however, that faculty with industry support were significantly more likely to report that their choice of research topics had been affected by the likelihood of commercial application. Most biotechnology faculty interviewed who do not receive industrial support believe that there has been a skewing of research toward the applied area, but the Blumenthal study

was not sufficiently fine-grained to determine the extent to which the research agendas of academic entrepreneurial scientists had shifted, if at all.

The second area of impact is the university. Much of the debate about university-industry ties has focused on how this will change university mores. Will the academic ethic that has nourished free and open inquiry give way to a new ethic of corporate-sponsored research? Will universities be a major producer of trade secrets? Will professors be judged on their ability to attract revenue-generating projects?

Although the evidence is incomplete, there are clear indications that academic research institutions have accommodated to industrial partnerships at the expense of traditional norms of scientific behavior. First, limited secrecy has replaced the unrestricted flow of information as an approved norm of scientific behavior. Included among the guidelines proposed by Varrin and Kukich (1985) for universities engaged in industry-sponsored research are the provisions that graduate theses containing patentable material may be sequestered for a year and that investigators be allowed to sign confidentiality agreements prohibiting them from divulging sensitive information for up to five years.

Most universities negotiating corporate research agreements have accepted publishing delays or even prohibitions where proprietary information is involved. The trend seems clearly toward practical compromise and away from the ideal of unfettered communication in science. For example, one of the surveys by Blumenthal et al. (1986b) found that increased industry sponsorship of academic research was correlated with increased secrecy in universities. Biotechnology faculty with industry support were four times as likely as those without support to report trade secrets (i.e., information kept secret to protect its proprietary value). One scientist interviewed by Etzkowitz concisely captured this new academic ethic as follows: "informing interested researchers without limit [is] a nineteenth century idea" (Etzkowitz, 1984, p. 8).

Second, universities have shifted their position on faculty entrepreneurship from neglect or even opposition to affirmative support. Several universities have actively invested in faculty enterprises and offered rental space for commercial ventures. According to Etzkowitz: "Some university administrators... are explicitly encouraging their academic staff to participate in industrial enterprises, viewing it as a contribution to economic development and as a means of gaining support for the university" (Etzkowitz, 1983, p. 222). Moreover, universities are increasingly prepared to modify their conflict of interest rules to accommodate commercial ventures (Kenney, 1986). For example, in founding the for-profit biotechnology firm Neogen in 1981, Michigan State University changed its conflict of interest rules to allow professors to acquire equity in the company while simultaneously serving as consultants to it.

In the past, faculty-owned firms were handled discreetly. Most universities had no restrictions against full-time faculty holding managerial positions. The case of Harvard Nobel biologist Walter Gilbert and his relationship to Biogen brought the issue to national attention. However, the debate over the Gilbert-Biogen tie did not extend to a dispute over the basic idea of faculty involvement in commercializing their research. Instead, the issue was the level of faculty involvement: whether full-time faculty should be permitted to serve as principals of firms; whether universities should be allowed to invest in faculty-managed firms; and whether such firms should be permitted to sponsor research on campus.

Varrin and Kukich (1985) recommend a compromise position: a faculty entrepreneur's company should not be permitted to sponsor his or her own research on campus, but the company should be permitted to sponsor other scientists on the cam-

pus, even within the same department. Under this norm, a senior faculty member with managerial responsibilities in a firm might serve the roles of both colleague and client with respect to a junior scientist.

Faculty Entrepreneurship and the Public Purpose

An issue that has received almost no attention in the debate about university-industry partnerships reaches beyond the norms of science and the mission of the university. I am referring to the importance to society of an independent academic sector. Professors are called upon to provide technical expertise and to exercise independent judgment across the range of public policy. Scientists serve on a labyrinth of public advisory committees and risk assessment panels at all levels of government. Every regulatory and funding agency depends upon the use of outside experts. For this process to work effectively in our highly complex technological society it is essential that we secure unbiased, objective advice from individuals who are financially disinterested in the areas in which they are called upon to consult. To take an admittedly hypothetical example, if every nuclear scientist in the academic world were concurrently on the payroll of the nuclear industry, where then would society find its disinterested nuclear experts? What confidence could we have in the objectivity of nuclear risk assessment? If we could no longer rely on the reports and testimony of academic scientists to assist elected officials in regulating nuclear power, we might well provide a cadre of nuclear scientists with public funds to ensure their independence from the nuclear industry.

This portrait of a commercially monopolized academic discipline is fortunately not applicable to nuclear scientists. But in other fields it may not be so far fetched. In 1969, Union Oil Company's offshore well sprung a massive leak in the Santa Barbara Channel. According to a report by Walsh (1969, p. 412):

> California's chief deputy attorney general...publicly complained that experts at both state and private universities turned down his requests to testify for the state in its half-billion dollar damage suit against Union and three other oil companies.

State officials attributed the difficulty they had in getting expert testimony to the belief that petroleum engineers throughout the California universities "did not wish to risk losing industry grants and consulting arrangements" (Walsh, 1969, p. 412). According to the report, academic scientists and engineers were part of an extensive university-industry "oil fraternity."

There is growing evidence that faculty-corporate relationships in biotechnology are manifesting similar patterns. As early as 1982, Culliton claimed that most of the nation's leading biotechnologists were affiliated with firms (1982, p. 960). In 1984, Zinder and Winn noted that very few hard estimates of faculty participation in commercially-related activities were then available. Since few universities require faculty to report such affiliations, and those that do insist that the information be kept confidential, institutions themselves are not good sources for this kind of information. Zinder and Winn were, however, able to obtain data on faculties at several West Coast universities which indicated that 12-15% of faculty in selected departments had consulting arrangements with the biotechnology industry. The authors claimed that this figure underestimates the actual extent of participation. They also cited testimony before the House Subcommittee on Investigations and Oversight by Natural Resources Defense Council attorney Albert Meyerhoff, who stated that nearly 100% of the top people in biotechnology are tied to firms (Zinder and Winn, 1984).

In the more recent studies by Blumenthal et al., (1986a; 1986b), 800 respondents were identified as working in the area of biotechnology. Among this group, 23% indicated that they were principal investigators on grants or contracts from industrial sources. However, the study provided no data on academic consultantships or faculty participation in biotechnology startups.

In 1984, at a Boston conference on Genetics and the Law, I reported preliminary findings on a quantitative study of professor-industry links in biotechnology. The study involved a data base of academic faculty and scientists at non-profit research institutes who meet one or more of the following criteria with respect to biotechnology firms: 1) serve on the scientific advisory board; 2) hold substantial equity; 3) serve as a principal. Academics who met any of these criteria were defined as "dual-affiliated" for the purpose of the study. The data base consisted of 345 dual-affiliated scientists (DAS) in 50 biotechnology firms. The information was gleaned from company reports and prospectuses. Data were provided on dual-affiliated scientists who are members of the National Academy of Sciences (NAS), who served on NIH study panels, and who were peer reviewers for the National Science Foundation (Krimsky, 1984).

Based upon data on a limited number of firms, I determined that 25% of the NAS membership in categories relevant to biotechnology had formal associations with the industry. I estimated that the figure could exceed 50% by the time all the firms were surveyed. David Baltimore of MIT and the Whitehead Institute responded that the figure is certainly higher than 50% (Milunsky and Annas, 1985). Bernard Davis of the Havard Medical School commented: "The situation, Dr. Krimsky, is worse than you think. The National Academy is a lifetime election with a large fraction of the members past retirement; for active members, it's way over 50% that have such connections" (Milunsky and Annas, 1985, p. 67).

Recently, the data base was expanded by surveying several hundred public and private biotechnology firms, and now comprises about 800 dual-affiliated scientists (DAS). The DAS comprise 30% of the NAS membership in biomedical science (over 100). Several of the leading universities have a sizable percentage of their faculty with commercial ties. Our figures include only scientists who have a "formal affiliation" with a biotechnology firm and exclude individuals who have grants or contracts but are not listed on the firm's roster. Therefore, the DAS data represent a lower boundary of university-industry affiliation. Many private firms do not publish their academic advisors, shareholders. or profiles and affiliations of managers. It is inarguably the case that the most prestigious universities in biomedical sciences have the leading scientists in the field and that the biotechnology industry has heavily contracted the services of these scientists. This fact is illustrated by the number of scientists at four leading institutions (Harvard, MIT, Stanford, and Columbia) who serve on advisory boards of biotechnology firms. The figures reported (see Table 1) are *de minimis* and probably understate the actual number of dual-affiliated scientists.

These data reveal the extent of the transformation in the biological sciences that has taken place since the discovery of plasmid-mediated gene transfer (recombinant DNA). Table 1 shows, for example, that Harvard has at least 60 of its faculty formally connected to 33 separate biotechnology companies, most less than ten years old. Previously, molecular biologists had very little commercial association. During the last decade, however, professors have started their own firms or, more frequently, been appointed advisors to new biotechnology companies. The pattern is similar, although on a somewhat smaller scale, at the other universities surveyed.

Table 1. Scientists with Corporate Affiliations in Biotechnology

Institutions	Number of Academic Scientists on Company Scientific Advisory Boards	Number of Companies Having Academics on their Scientific Advisory Boards
Harvard (all schools)	60	33
MIT	33	24
Stanford	35	19
Columbia	18	14

I have argued elsewhere (Milunsky and Annas, 1985) that heavily commercialized disciplines may be a social liability. It is vital to the public purpose that a critical mass of scientific specialists remain disassociated from industrial ties in areas related to their field of expertise (Krimsky and Baltimore, 1980). In biotechnology, it is questionable whether that critical mass still exists, at least among the leaders of the field. A few quotes from a recent editorial in New York's *Newsday* illustrates that the suspicion of the scientist-extrepreneur runs very deep in the mass media:

> A number of (Genentech's) stockholders are principal investigators in a federally sponsored $31 million clinical trial of a hot new Genentech product called TPA, an anti-blood clot drug. If the study convinces the government that TPA is safe and effective, Genentech will make a bundle...Mount Sinai Medical Center and 16 other hospitals agreed to share in profits that might come from an experimental drug they're testing for the relief of symptoms associated with Alzheimer's disease. And last month, a Harvard scientist presented a paper at an international conference on Lyme disease praising a new method for controlling illness-transmitting ticks. He failed to disclose that he is founder and officer of the only company that markets this method...It's time for the government and academic institutions to stiffen their attitude toward conflict of interest. The public's health depends on unbiased results free of even the appearance of ulterior motives in testing (*Newsday*, October 16, 1987).

In order to avoid even the appearance of impropriety and the self-aggrandizement of expertise, the ties of scientists to commercial institutions related to their research must be publicly disclosed. Disclosure does not solve the problem of preserving a disinterested pool of scientists, but at the very least it is information that a responsible electorate and its representatives will need in order to render informed decisions.

Conclusion

Earlier in this paper, I introduced the metaphor of multiple personalities as a heuristic device for understanding the changing relationships that have evolved among universities, government, and the commercial sector. The metaphor highlights the fragmentation and, at times, the conflict of purpose within institutions of higher learning. By embracing several identities, universities can capitalize on diverse funding sources, can accommodate a faculty that values its freedom of association, and can respond to a national challenge that seeks to foster technology transfer as a means of improving America's global industrial position.

Multiple personalities are adaptive to universities. Each of the four forms of institutional identity serves a function. The identities generally coexist in reasonable balance.

But the rapid commercialization of biology has led some critics, inside and outside of academe, to question the reconstruction of this balance. When the balance is challenged, as it has been in the media and from some sectors of academe, it reminds us that the identity crisis within universities is a reflection of broader societal issues. Each of the institutional "personalities," after all, is derived from a public purpose. Universities cannot serve all purposes maximally and still retain a set of coherent values. However, among its four "Personalities" there is one which is distinctive. Without a strong classical identity, a university loses its unique status in society. It becomes a handmaiden to special interests. This may be the outcome of the social evolution of the university. In such circumstances democratic societies will have to invent surrogate institutions to replace the loss.[2]

Notes

1. For a more extensive discussion, see Krimsky (1987).
2. I wish to thank James Ennis of Tufts University and Robert Weissman of Harvard University for their help in developing the data base from which some of this analysis was derived. Sections of this paper are adapted from Krimsky (1987).

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Academic-Corporate Interactions: Is There an Indirect Alternative?

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Both the opportunities and problems presented by the increasing interaction between universities and industrial corporations have been much discussed over the last few years, particularly in connection with the new biotechnology. In addressing the subject here I make no claim to be comprehensive or detailed. Rather, my purpose is to make several selected points, leading toward a single important recommendation.

Given the complications and potential negative consequences of **direct** academic-corporate interaction, it may be advantageous to consider **indirect** interaction through an intermediary mechanism of broader scope. Such a mechanism might also help resolve certain severe structural limitations preventing adequate funding for fundamental science, and contribute to more rapid information transfer from basic science to economically productive technology. In this paper I will detail some of the shortcomings of the current funding mechanism and the ways in which my proposed indirect alternative would overcome them.

Industry As An Alternative to Government Support

The unprecedented and inspired mid-century policy decision by the U.S. federal government to invest heavily in the support of basic research provides essential background to the current controversy over direct academic-corporate interaction. In essence, that decision established a fundamental principle – **science and technology are too central to the national welfare and too expensive in necessary investment to be left primarily to private direction and support.**

Cellular and molecular biology were among the basic research areas to flourish through federal support, specifically from the National Institutes of Health and, to a lesser extent, the National Science Foundation. With a shortening of the path from theory to practice in these areas of biology, a number of inviting new practical applications emerged, particularly in medicine and agriculture. Since, in the U.S., theory has been primarily an academic function and practice primarily a corporate function, newly formed interactions between the academic and corporate worlds quickly followed, resulting in the flowering of the "new biotechnology" by the early years of this decade.

During this same period, in biotechnology as well as other areas, important changes were occurring in the national pattern of R&D support. National policy and budgetary emphasis shifted significantly from fundamental toward applied research and from civilian to military applications. This shift has had a serious impact on research-oriented universities whose research staffs and facilities were largely brought into being through federal encouragement and largesse. These universities saw expanded corporate relationships as an attractive alternative source of supplementary resources for the institutions and individual faculty members alike. One of the most important potential sources of support might be found in the emergence of corporate biotechnology, where

fledgling firms were looking not only for venture capital but also for access to the frontiers of biological science. The result was a rush to establish new relationships between individual universities and biotechnology firms.

Despite enthusiasm over this apparent synergism between academic and corporate capabilities and needs, the relationships are by no means unanimously viewed as entirely beneficial, and they have not yet yielded a bonanza for either universities or corporate investors. Although some new research facilities have been built and some practical applications of new knowledge have undoubtedly been accelerated, the problems of aging physical plant, access to state-of-the-art equipment, and stable career funding for basic science investigators continue to plague national science policy.

Moreover, there is growing concern in both academic and corporate circles about certain negative aspects of the trend toward increased academic-corporate ties. It has been noted, for example, that current anticipation may far exceed future reality in terms of the amount of resources that may be generated from industry, particularly if federal support, which has traditionally been more than ten times greater than that provided by industry, were to be correspondingly trimmed. Another set of concerns which continues to be raised in the academic community relates to the impact of corporate ties on the central academic role – emphasis on the free, open, and objective pursuit and dissemination of knowledge and understanding. These concerns can be expressed through a modification of the fable of the goose that laid the golden eggs. Would a goose fathered by a corporation and mothered by a university – or vice-versa – continue to lay eggs and, if so, would the eggs be golden, or brass, or even mere dross, in terms of fundamental academic values?

The Science-Technology Axis

Beyond those concerns which deal specifically with academic-corporate hybridization lie broader and more fundamental societal issues. For example, it is an obvious fact that, as this century has advanced, science and technology have become inextricably intertwined as a driving and generative economic axis. Scientific advances spawn new technologies (e.g., biotechnology) and new technologies advance scientific frontiers (e.g., genetic engineering). Out of the dynamism of this powerful positive feed-back mechanism there frequently emerge new technologies of production to meet human needs (e.g., industrial production of genetic recombinants).

Unfortunately, the upward spiral of the science-technology societal axis often generates unwanted secondary consequences. It has been extremely difficult to date to mitigate appreciably such consequences, much less to avoid or eliminate them altogether. Like the cost of meeting human wants and needs and the cost of dealing with the social and physical consequences of new technologies, the cost of conducting research and development has skyrocketed. To illustrate, the price of each new informational bit of knowledge, whether fundamental, diagnostic or industrial, rises steeply as one seeks it more deeply or more widely. In this sense, delving more deeply into the elementary structure of matter is analogous to drilling more deeply for oil. And witness also super-computers, super-colliders, and space-shuttles.

Although the above problems are widely acknowledged, there is no significant agreement – whether in the United States, the Soviet Union or the developing world – that their solution would justify slowing or stopping the dynamic spin of the scientific-technological axis. On the contrary, most of the world's nations, whatever their social, political, moral, or economic philosophy, seek new ways to couple more effectively to the

dynamism of the axis, whether for peaceful or military purposes. Whether in the geographic or political East, West, North and South, there is intense rivalry to exploit science and technology for economic gain. All regions agree that the axis should spin as fast as possible.

Even though fundamental science and technology (to say nothing of manufacturing and marketing) are thus intertwined, in the U.S., at least, they flourish in different social, political and economic niches. It is not clear whether, if the normal niches for the two were exchanged or if a hybrid of the two were created, scientific or technological advance would be positively or negatively affected in the long run. It is certainly still reasonable to ask whether such changes would weaken or possibly kill the golden goose of science and dissipate the energetic practical thrust so prized by and remunerative to corporate enterprise.

Furthermore, in considering such changes, it must be kept in mind that both universities and corporate structures have more than one function. Universities provide not only the primary site of research laboratories, they also constitute the most important educational seed-bed. While they initiate discovery, they also seek to transmute discovery into wisdom by melding knowledge with values. Out of this generative seed-bed emerge not only scientists and technologists, but also citizens, teachers, doctors, lawyers, corporate managers, and political leaders. Because universities not only promote the pursuit of substantive knowledge but are a fount of intellectual clarity, they play a vital role in the formation of each generation's societal decision-makers as well as researchers. Among the most important tasks for decision-makers of the coming generation will be to figure out how better to shape science and technology to human purposes.

Similarly, the corporate world has more than one function. It not only nurtures the academic eggs until they hatch as technology, it also distributes in the form of profit (and taxes) the added economic value they create, assuming they turn out to be golden. For investors, and thus for corporate management, this is, of course, the major motivation for their nurturing role. Inevitably, however, this motivation significantly channels corporate enterprise toward relatively short-range objectives that will yield relatively quick and certain return. The profit motivation influences their emphasis on consumer end-products and also their participation in the innovation and expansion of technology itself.

These distinctively different, but also overlapping sets of roles of academic and corporate structures complicate and limit their miscibility. Were academic institutions solely involved in expansion of fundamental knowledge and corporations solely devoted to its application (an over-simplification frequently indulged in during discussions of knowledge and technology transfer), it would be much easier for the two to bond at their interface. The traditional academic emphasis has been on free inquiry, openness of communication, and the assumption that benefits will flow from research over the long run. Such concerns are not easily encompassed within the corporate emphasis on focused effort directed toward short-term pay-back measured at the bottom line. Corporations have been less concerned with open communication than with limiting communication to those who need to know in order to achieve corporate objectives. In contrast, the details of product marketing are of little concern to university faculty, except perhaps in business administration programs. There may be specific situations where the very different operational styles and motivations of academic and corporate worlds can be accommodated in a common milieu. But can this be accomplished widely and generally without unacceptable sacrifice of essential norms and practices in both sectors?

Inadequate Mechanisms for Supporting Basic Research

It is just here that the structural problems inherent in current mechanisms for support of basic research are most significant. The major mid-century policy decision that led to massive public funding for fundamental science was made in furtherance of the concept of the welfare state. That concept provides for government action to ensure the welfare of those designated as needy and deserving of societal support, including the poor, the ignorant, the dispossessed, those who drive trucks on inadequate highways, and those who farm on economically marginal land. Under the welfare concept, taxation produces revenue flowing to the national treasury. The federal budget then distributes largesse, along lines determined by negotiation between the President and Congress, to those groups defined as deserving of support. It should come as no surprise that this process has resulted in endless political wrangling and in allocations that are always lower than judged necessary by those who feel themselves in need.

Over time, the process leads, logically and inexorably, to a negotiated plateau for any particular item in the federal welfare budget. In recent years, with economic stringency stimulating efforts to cap discretionary spending, the pain experienced by recipients of federal welfare funds has intensified. Science did reasonably well for perhaps two decades due to its acknowledged importance to national security, human health, and other policy goals. For the most part, however, it has recently succumbed to the limits imposed within a closed budgetary system governed by zero-sum negotiation. A glance at current budget proposals reveals that the major exceptions are medical emergencies (Acquired Immune Deficiency Syndrome), targeted programs for security (Strategic Defense Initiative) or prestige (Superconducting Supercollider), and pork barrel scientific and engineering projects. Basic science in general has joined social security, highway maintenance, and aid-to-dependent children as discretionary programs scanned for budgetary savings.

Clearly, the current mechanism whereby funds for scientific research are appropriated and allocated is inadequate, given the dramatic change in the role science plays in the economy. The welfare state has been transformed into a technological state driven by scientific discovery with basic research at the foundation. Incremental economic value resulting from industrial production, whether in the form of consumer products, expansion of productive plant, or military security, is derived indirectly from the science and technology axis, whose foundational thrust is basic science. What should be the driving force of the economy is hobbled by a budgetary process which is now increasingly "capped" and which requires every line item to compete with every other in terms of immediately perceived overall welfare requirements. Under the current process, dire and immediate necessity becomes the top qualifying standard.

But fundamental scientific research has difficulty justifying itself on grounds of dire and immediate necessity. It is not a criterion that can be applied to activities that may take one to three decades to be realized, but at a level several orders of magnitude greater than the initial investment. **Therefore it is time to rethink budgetary strategy for science and technology in ways that are more appropriate for a society that is driven by dynamic and open aspirations and values, rather than those which characterized the closed traditional welfare state.**

A Proposal

For a technologically advanced nation, seeking to maintain its leadership role in a problematic world order, basic science is a primary foundational value because it creates

information and knowledge that is transmuted technologically into economic productivity. Some portion of that variously value-rich product generates enormous economic return through technological innovation. **To continue to generate this return in rising measure, the level of investment in basic science can no longer be limited by the politically competitive trench warfare inherent in traditional welfare-oriented budgeting.** Instead, expenditure for basic science must be commensurable with its status as the foundation line for value-generation in a value-oriented economy. In short, basic science must be treated as a national resource and not as a social service.

This translates into the proposition that, as value is realized through science, technology, and production, a suitable fraction of that value should return by direct feedback, not only to assure maintenance of the scientific enterprise, but to assure real growth in basic scientific activity to energize a growing economy. In these terms, the appropriate level of support for basic science should not be measured as a fixed fraction of the total federal welfare budget but as a fraction of the value generated by science and technology as applied to economic production. Moreover, the size of the fraction going to scientific research should be based not on speculative prospective projection of future value added, but on retrospective analysis of the actual historical track record.

Direct positive feed-back of value earlier created by science and technology should begin with sequestration of a fraction of that value in a **National Science and Technology Fund**. In the conceptually simplest way (though not necessarily the most feasible politically), a fixed percentage of income clearly traceable to contributions of basic science would be assessed on behalf of the Fund against corporate taxes collected from those industries that are substantially based in scientifically derived technology.

The Fund might be administered by a federally established Board of Trustees charged: 1) to promote and finance basic scientific research in all effective ways; 2) to facilitate its dissemination and application; and 3) to widen public understanding of the values and issues which arise out of scientific and technological advances. The Board could also be charged with specific responsibility for ensuring the vigor and health of the national economic enterprise based on science and technology, perhaps in cooperation with the National Science Board of the National Science Foundation.

Thus, the Fund would serve, in part, as an indirect pass-through for generated value between academic and corporate sectors without large scale mating between the two. On the one hand, it would fund economically relevant basic research and further its dissemination to industry. On the other hand, by avoiding unnecessary overlap of academic and industrial activities, such a system would reduce concerns about blending two cultures that have been successful in the past in their separate and relatively independent milieus. To emphasize the importance of rapid information transfer from discovery to application, the Fund directors might be specifically charged with encouraging various forms of interchange of individuals and information among the critical sectors of the science-technology-production axis.

The mechanisms outlined have several additional strong advantages. First, they set no target for, and thus require no forecast of, the actual value to be generated by new basic science. Rather they call for a set-aside of a fraction of the value **already** generated. Even if a five-year delay in collection were to be stipulated to offset start-up costs of innovative technology, return to the Fund would be substantial from the beginning, and could be expected to grow rapidly by the end of a decade of operation.

Second, the proposal recognizes that the time and manner of economic pay-off for individual items of basic science are unpredictable, but that the pay-off from the totality of basic science is significant and assured, as amply demonstrated by the track record of

the last half-century. Specific proposals for basic research support, therefore, would not need to be justified in terms of the economic return each would provide, but could be evaluated entirely on the basis of their intrinsic scientific merit.

Third, by providing a new and differently oriented channel for support of basic science, the Fund could concentrate on types of research and objectives that tend to be overlooked by the existing highly institutionalized and somewhat rigid mechanisms. It is, for example, often alleged that highly imaginative interdisciplinary research proposals are disadvantaged in the present disciplinary climate of support of basic science by federal agencies.

Fourth, the secondary impacts of advancing science and technology, currently plaguing regulatory agencies and the courts in connection with health, environmental impacts, and resource planning, might be more effectively anticipated if funds were made available for the early assessment of new scientific trends and developments and the technologies they spawn.

Summary

In considering the relationships of academic and corporate scientific and technological activities, it is important to provide that these relationships facilitate and promote rapid application of new fundamental science. This is an essential national objective. However, the best way to do this may not be to blend, simplistically and without limit, the very different environments of academic and corporate life. Rather it may be more effective to maintain a degree of structural separation while providing feedback of technologically derived value to the basic science seed-bed. This would be done through a set-aside of a fraction of science-based corporate taxes to a National Science and Technology Fund external to both academic and corporate decisions.

Trustees of the Fund should be charged to serve general societal interests. In addition to allocating supplementary funds for basic science, their mission might include promoting information transfer at the academic-corporate interface in ways that would speed new discoveries into application, but without excessively merging the different and separately successful academic and corporate milieus.

What's Really at Issue in the Controversy over Corporate-University Ties?

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The five papers in this collection are a significant contribution to the "debate" over corporate-university research relationships. They contribute by revealing something less than a debate. There are sides, to be sure. Roger Beachy, Edward MacCordy, and Jeffrey Price all praise the increasing cooperation between universities and corporations, while Sheldon Krimsky and Clifford Grobstein both criticize it. Yet, we have only to look at what the five say to see that they do not address each other's arguments as parties to a continuing debate generally do. If the controversy over corporate-university ties is less than a debate, what is it? Before considering that question, let's look at what the parties actually say.

A Brief Look at the Controversy

Those favoring corporate-university ties describe their own favorable experience. Beachy describes his industry-supported research, stressing especially the two-way flow of information, skill, and stimulation. MacCordy describes a similar process of mutually beneficial cooperation, but his perspective is that of a university administrator rather than of a researcher. And Price, a corporate official, gives a strikingly similar report. For all three, ideas, technology, and discoveries rather than money are the primary currency by which corporate-university cooperation pays for itself. In this respect at least, corporate-university ties look little different from ties between, say, a chemistry department and a chemical engineering department within the same university; corporate-university ties look like nothing more than cooperation between organizations with somewhat different emphases.

Beachy, MacCordy, and Price do not claim that corporate-university relationships are trouble free. Indeed, each discusses problems he has experienced. All three seem to recognize that such problems arise because corporations are more likely to want to keep information secret than universities are, because university researchers are less concerned to see immediate practical results than corporate researchers are, because corporate researchers are likely to forget that university researchers are responsible for the welfare of the graduate students they employ, and so on. But, for Beachy, MacCordy, and Price, the problems are practical ones they have been able to resolve case by case, not systemic problems compromising any important principle. For these three, the fruitfulness of corporate-university relationships more than compensates for the trouble they must take to resolve such problems.

Neither Krimsky nor Grobstein denies that corporate-university ties are generally fruitful. Indeed, Krimsky cites without objection substantial empirical evidence of that fruitfulness. Rather than deny anything Beachy, MacCordy, or Price says, Krimsky and Grobstein devote much of their papers to issues about which the former say nothing.

Krimsky, a philosopher of science, argues that corporate-university ties tend to destroy the university's ability to serve the public. Close ties between corporations and universities, however fruitful, generate too many conflicts of interest. University researchers with corporate ties hesitate to publish their discoveries, to share raw data, to speak out on behalf of the public. They lose their status as independent experts. University-corporate collaboration means that the university may have to give up certain of its traditional functions.

Like Krimsky, Grobstein describes certain changes corporate-university ties could bring about, but Grobstein's concern is that, however fruitful particular corporate-university ties, in the long run they may destroy the university's ability both to **train** basic researchers and to **do** basic research. Corporate-university ties threaten the university as we know it.

But Grobstein, himself a university biologist, proposes an alternative: to make corporate-university ties less necessary—and so, less common—by taxing high-tech corporations to fund university research. If his proposal succeeded in this, it would automatically make less common the conflicts of interest Krimsky is worried about. Though Grobstein and Krimsky do not always sound as if they agree about the problem, the points of agreement are more important than any disagreement.

That, then, is the "debate" between these five papers. There seems to be no **clear** disagreement about any matter of fact or principle. What about the controversy over corporate-university ties might explain the failure of the sides to engage? That, I believe, is **the** crucial question. If we can answer it, we should be able to bring the controversy to a close or, at least, to understand why it cannot be closed. Because I believe the question to be crucial, I shall try to answer it here. My answer is that what is really at issue is our conception of science. I shall try to show this by analyzing the five papers to reveal the assumptions underlying what they actually say. What follows is meant to be suggestive, not definitive.

Assessing the Critics

Because the assumptions of the two critics of corporate-university ties are more explicit than the assumptions of the three defenders, I shall examine the Krimsky and Grobstein papers first. And because Krimsky makes the useful suggestion that we try to understand the controversy in terms of the "university's multiple personalities," I shall begin with his paper.

Krimsky distinguishes four "personalities" of the university: **classical**—knowledge as virtue; **Baconian**— knowledge as productivity; **defense**—knowledge as security; and **public interest**—knowledge as human welfare. For our purposes at least, these four "personalities" may be reduced to two, the classical and the Baconian. Bacon, after all, understood knowledge as a "power" of which productivity, security, and public service would be no more than three consequences. For a Baconian, a conflict between, say, knowledge as productivity and knowledge as public service is simply a practical problem of how much of each we, the public, want. Because productivity as well as public service is generally in the public interest, compromise is altogether appropriate. We may, for example, have to give up some productivity to maintain a certain reservoir of independent experts available for public service.

Disagreements between the classical conception of science and the Baconian are not like that. Consider, for example, this classical expression of concern about corporate-university ties:

> This journey of discovery can only be undertaken once, and it would be better undertaken by people who have no interest in anything but discovering the truth, whose hands are clean, whose motives can never be criticized...And if commercialization...ever starts to infuence the scientists' primary goal...then the scientists themselves [will] I hope...have the sense to put a halt to it. (Lappé, 1984, p. 281).

Like Krimsky, this writer (the molecular biologist Jonathan King) is concerned with conflict of interest. But the concern is not merely that the public will lose a certain reservoir of independent experts. The concern is that science itself will be deflected from its goal of "discovering the truth." Since, according to this writer, discovering the truth is "the primary goal" of science, a scientist with an "interest in anything but [that]" will not have "clean" hands. He will have compromised an important principle of science.

I initially thought of the classical conception of science as favoring "basic," "pure," or "fundamental" research over "practical" or "applied." I now see that thinking of the classical conception in that way is a mistake. Grobstein, especially, has no objection to applied research within a university so long as those doing it are concerned with the research itself rather than with (in Grobstein's own words) "short-term pay-back at the bottom line." What seems to concern Grobstein is not so much relations between basic and applied research as between (what we might call) "inquiry-driven" and "market-driven" research. Grobstein wants to keep market-driven research at a safe distance from the university, the "seed-bed" of inquiry-driven research.

Grobstein does not object to the discoveries of science being put to practical use. He can sound positively Baconian, for example, when comparing science to the fabled goose that laid golden eggs. Indeed, his worry is that university science will not lay golden eggs in an environment in which profit is an important motive. Grobstein does not, however, offer any empirical evidence for that worry. Since the question of what motives have made for the best research remains a vexed question in the history of science, it is not easy to marshal **empirical** support for Grobstein's position.

While Grobstein's worries don't suit a Baconian, they do suit someone with a classical conception of science. For example, for someone with a classical conception, corporate researchers would necessarily be a breed apart because their market-driven research is fundamentally different from the traditional inquiry-driven research of the university. To combine market-driven and inquiry-driven research is to create a "hybrid," as Grobstein calls it, temporarily vigorous perhaps, but likely to be sterile in the long run.

Grobstein's concern that corporate-university ties will threaten the very "fount for intellectual clarity" can, I think, also be seen as an expression of the classical conception of science. A Baconian would not expect proximity to commercial research to threaten intellectual clarity. Quite the contrary. Such proximity would help "citizens, teachers, doctors, lawyers, corporate managers, politicians and statesmen" understand science better. They could see more clearly the alchemy by which science becomes power. Only the classical conception of science would make proximity to commercial application seem a problem.

Grobstein's solution to the problems he identifies also seems an expression of the classical conception of science. He does not ask what effect a tax on the use of basic research would have on commerce, on corporate research, or on anything else external to the university. His focus is on the effect the income derived from such a tax would have on research **within** the university, the traditional home of science classically conceived. For this purpose, he seems to think of the university as a single organism rather than as so many water-tight departments, specialties, or labs. He seems to doubt that market-driven

researchers can share a department or school with inquiry-driven researchers without substantial harm to the climate of research.

Grobstein believes that more money for university research would mean less cooperation between corporations and universities. Why? If the primary reason university researchers are willing to mix with corporate researchers is that they need the money corporations can provide, then the tax will indeed drastically reduce corporate-university ties. If, however, that is not the primary reason university researchers mix with corporate researchers, then Grobstein's new money may have little effect on corporate-university ties. A classical conception of science would naturally lead someone holding it to suppose that money for research must be the dominant motive an inquiry-driven researcher could have for mixing with mere market-driven researchers.

A Baconian or Classical Approach?

Though Grobstein seems to suppose that money for research must be the dominant reason that university researchers are willing to enter into corporate-university research relations, we need not agree. The theme common to Beachy, MacCordy, and Price is that money is not the dominant motive for corporate-university ties. University researchers benefit from close cooperation with corporate researchers in ways for which money can provide no substitute (for example, insight into applications, leads on new technology, or a different perspective on a common problem). Insofar as that is so, Grobstein's tax can have little effect on corporate-university ties.

So, for Beachy, MacCordy, and Price, Grobstein's proposal must seem little more than an unlikely way to increase funding for university research. As Baconians, they need not oppose such new funding so long as university researchers remain as free to cooperate with corporate researchers as they are now. For a Baconian, the only objections to Grobstein's proposal would be practical. Can the calculations he calls for actually be made? Would Congress be willing to adopt a new tax on the scale Grobstein proposes? Would the tax seriously handicap American high-tech industries competing with industries not so taxed?

We have, then, two ways to approach corporate-university ties. We can, first, approach them as Baconians, seeking practical solutions to the problems Krimsky and Grobstein have identified. (For example, we might propose editorial rules requiring academic researchers to state their commercial interests when they publish their research, as a way to resolve one conflict of interest Krimsky identified.) We would seek to get as much corporate-university cooperation as possible consistent with other interests we have.

That is one approach to corporate-university ties. The other presupposes a classical conception of science. This second approach would require us to view any mixing of the two "cultures" as in itself dangerous and seek to keep it to a **minimum** consistent with other interests we have. We would not seek practical compromises between corporate and university practices. We would view such compromises as violating an important principle: **Research should be driven by the logic of inquiry, not the oportunity for profit.**

Conclusion

Which approach should we take? That question will have no final answer without much more research into the history, philosophy. and sociology of science. What are we

to do in the meantime? All that we **should** do, I think, is what the major research universities have been doing so far. On the one hand, we should recognize that Krimsky and Grobstein **could** be right. A fundamental principle could be at issue whenever market-driven research has a substantial presence in a university. But, on the other hand, we should recognize as well that Krimsky and Grobstein **could** be **wrong**. The only problems university-corporate cooperation raise could be the practical ones Beachy, MacCordy, and Price believe themselves to be resolving one by one. We should not stand in the way of **good** research even if it is in part market-driven. But we should (as Beachy, MacCordy, and Price all seem to) recognize a standard of good university research other than "whatever the market will bear." We should avoid adopting policies that presuppose more than we in fact know. We should, in short, try to muddle through.

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Afterword

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The papers collected here present a series of illuminating perspectives on the proliferating academic-corporate relationships of the 1980's in biotechnology. The three first-hand accounts by reflective participants, Edward MacCordy, Jeffrey Price and Roger Beachy allow us to gauge what qualified insiders regard as new and valuable, what they see as pitfalls, and perhaps what they fail to recognize as pitfalls or risks. The critical observers, Clifford Grobstein and Sheldon Krimsky, urge us to consider what losses we may sustain from the closer ties between academia and commerce. Michael Davis offers a philosophical analysis of what is at issue in the concerns of critical observers who are keenly aware of the general satisfaction of the participants.

What follows is another focus for assessing the new relationships and reflecting about the critical concerns expressed in this volume. The emphasis is on informal rules or norms. One is struck by the participants' avowal of traditional norms and standards and their insistence on their ability to maintain these norms and standards in the face of new institutional arrangements and often very high financial stakes. This confidence reminds one of classroom discussion about professionals accepting gifts which might influence judgment. Often a student will insist, 'I could accept that gift and still render independent judgment.' An outsider's doubts need not reflect any question about the recipient's sincerity. Doubts rest on what we know generally about people in such circumstances and about familiar barriers to our making impartial judgments about ourselves.

There is wide agreement on a set of norms and values that were presumed to govern conduct in academia. A commitment to openness is probably the most central and salient. It implies respect for instructors' free expression in the classroom and the expectation that research results will be published and disseminated without restriction. Reasonably well defined informal assumptions about the treatment of graduate students supported respect for them as dependents and colleagues.

We may wonder whether conformity to these standards of openness and respect was ever as extensive or complete as many assumed. Nevertheless, it is reasonable to doubt that the informal norms that did operate can be carried over to the new relationships without serious strain. Those doubts are fueled when one hears an experienced university administrator of research comment that, in negotiations with companies, he has to press faculty to hold out for a tougher stand on open publication. A faculty member will say, 'I never published in that area anyway.' Reports of competent graduate students requiring exaggeratedly long periods of time to complete dissertations support concerns about the exploitation of graduate students. Again these worries are based on general knowledge of how people will be tempted to behave when practices are changing.

It is possible, of course, that the concern recently generated about delays in publication, discharge of academic and collegial responsibilities, and treatment of graduate students may positively affect conformity to norms which had been assumed to govern. However, in light of the swift changes brought by the new relationships, one suspects that older norms, which made certain conduct reasonably predictable, are eroding. The

pace may be slow enough for the participants, and others, to fail to discern the changes, but the shifts may be significant enough to justify concern.

In the history of science since the seventeenth century, the dependence of scientists upon patrons with needed financial resources is hardly a new phenomenon. In marketing himself, Galileo could point out the benefits his telescope would bring to his patron. It appears that scientists succeeded often enough in working out an accommodation that satisfied their patrons and maintained the openness needed for cumulative development. We are led to ask whether, even now, new or altered norms are emerging which will also yield a satisfactory accommodation.

In the light of that question, it is interesting to note in Beachy's account that graduate students and post-docs were initially put off by Monsanto's need to withhold information for proprietary reasons. This reaction was blunted, he suggests, by the ongoing open communication between university and company researchers within the framework of secrecy. By the time jointly authored papers were published, the junior investigators in the university had largely accepted the terms under which they pursued their research.

However, as Beachy and Price emphasize, research team leaders in the university and the company must be vigilant to maintain the conditions on which trust and openness within the collaboration are founded. Here the research directors seem to be breaking new ground. Particularly important is the practice of assigning credit across institutional lines in the ultimately published work. Nevertheless, Beachy and Price concede that publication delays on proprietary grounds pose risks for young scientists. Beachy indicates that research directors on both sides must, in the process of communicating and sharing information, stay alert to the need to separate what will be made public eventually from what must be withheld. We have no basis for questioning his claim that it is readily apparent what information falls in each category. One wonders, however, to what extent this vigilance on behalf of protegès is dependent upon the particular character of the research director. If the character of the research directors is critical, we have to ask what in their circumstances or prior preparation supports the expression of the appropriate character traits.

From his vantage point as a university administrator, MacCordy surveys problems and pitfalls of university-industry research relationships. He puts his trust in formal guidelines and properly negotiated agreements to avoid serious problems. The question remains whether these measures can sustain the appropriate informal norms. The question is based on general knowledge, particularly about the power of certain temptations created by the proximity to commercial attitudes and practices. The desire of both negotiating parties to maintain the distinctive character of the participating organizations may not be enough to enable university scientists to withstand the pulls of commerce when new associations and practices are introduced. This is why skeptical doubts remain even when observers point out that research universities are often in strong bargaining positions (Etzkowitz, 1983).

Jeffrey Price contributes a picture of the research atmosphere in the new biotechnology companies. He points to evidence of some capacity of university norms to migrate to industry under certain conditions. However, his account of the movement of scientists back and forth between the corporate world and academia and his description of scientists with a foot in each world engender questions about how individual scientists adapt to the contrasting norms of these worlds. How firmly do these scientists identify with the values and norms of academics? How readily can they separate their activities in one sphere from their activities in the other?

In Price's experience, university-industry relationships develop from successful individual collaborations between particular scientists. This pattern brings out the importance of informal norms, for in these individual collaborations much depends upon a scientist's own ingrained ways of behaving. Price emphasizes that companies do not seek to change the ethos of universities or the orientation of university scientists. Indeed they recognize their own stake in the maintenance of university research traditions.

We are left with a sense of both the adaptability and the fragility of certain informal rules of conduct which have been important ingredients in a successful, largely open scientific enterprise. Accommodation of these rules to new collaborative arrangements is underway. The questions generated here about this process of accommodation surely merit follow-up investigation.

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PART II

Responsible Uses of Microorganisms and Microbiological Products

Contributors

Roy Curtiss III, a microbiologist, founded in 1981 the University of Alabama's Cystic Fibrosis Research Center and served as its director. In 1983, he moved to St. Louis where he became George William and Irene Koechig Freiberg Professor and Chairman of the Department of Biology at Washington University. He has conducted research on the genetics of bacteria and their viruses for many years, and is currently investigating the molecular genetic basis of bacterial pathogenicity and is developing new strategies for production of recombinant live vaccines to prevent infectious diseases.

David A. Fischhoff has been a postdoctoral Fellow in yeast molecular biology at Washington University in St. Louis and for the past five years has been a research scientist at Monsanto Company. He is currently Project Leader for Insect Tolerant Plants in the Biological Sciences Department at Monsanto.

Jeanne S. Poindexter is Associate Professor of Biology at the Brooklyn Center of Long Island University. She serves on the American Society for Microbiology's Committee on Ethical Practices and Committee on Environmental Microbiology. For several summers, she served as resident instructor in the microbial ecology program at the Marine Biology Laboratory, Woods Hole, MA. Research interests include microbial ecology of aquatic habitats, microbial adaptations to nutrient limitation of growth, and relationship of morphogenesis to nutrient scavenging in stalked bacteria.

Chet Roberts is a Lieutenant Colonel, Medical Service Corps, U.S. Army, assigned to the Walter Reed Army Institute of Research. He works in the Institute's Division of Retrovirology, where he is involved with research on human immunodeficiency virus (AIDS). Formerly, he served at Headquarters, U.S. Army Medical Research Development Command.

Lidia S. Watrud has been with Monsanto Agricultural Company since 1975, where she is currently Manager, New Technologies, in the Plant Sciences Department. In previous positions with Monsanto, she has served as Manager of the Environmental Microbiology Group and of a Molecular Biology Group. She has a long-term research interest in the physiology, genetics and ecology of plant-microbial interactions.

Responsible Uses of Microorganisms and Microbiological Products

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In 1984, the American Society for Microbiology formally adopted a Code of Ethics for professional microbiologists (*ASM News*, 1985). The first principle of the Code states, in part, that microbiologists "will use their knowledge and skills for the advancement of human welfare," and the first Canon states that "Microbiologists recognize a duty to the public to propagate a true understanding of the science. They will avoid making statements known to be premature, false, misleading, or exaggerated and will discourage any use of microbiology contrary to the welfare of humankind. They will work for proper and beneficent application of scientific discoveries and will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology." These statements illustrate the attitude of the Society regarding the relationship between professional microbiology and public concerns about practices that employ invisible, but very influential living organisms, i.e., microbes.

In a decade that has witnessed the advent of an infectious disease that seemingly irreversibly disables the human immune system, biologists and public alike have grown in their awareness that the microbial challenge to human health is constant. We have been reminded that individual freedom from disease depends on the normal, unceasing defense of the immune system, even in societies where general vigilance regarding the public health has resulted in a virtual disappearance of microbial and viral infections as major causes of death, particularly of "premature death." We have also learned that microbes previously regarded as innocuous can, in the immune-disabled individual, cause fatal infection. The distinction between pathogen and non-pathogen has become less dependable, just at a time when developments in the molecular biology of microorganisms and viruses have encouraged the expectation that the beneficial uses of microorganisms and their products can be increased.

Among these uses are applications in ecology, particularly in agricultural systems. The public is properly concerned that spraying microorganisms over vast areas of cultivated land could have unexpected and possibly adverse effects on the environment, on livestock or—the principal concern—on humans. While employing microorganisms (mainly bacteria) to inoculate crop plants is not a new practice and has been used for most of this century (and earlier; see, e.g., the lively review of nitrogen fixation by P.W. Wilson, 1963) to increase productivity of certain crops, concerns are largely a reaction to proposals to use microorganisms modified by recombinant-DNA technology, so-called "genetically-engineered microorganisms" (GEMs). GEMs are intentionally constructed to be different from naturally-occurring microbes; they are altered to improve their ability to perform a given task, much as human workers are instructed or computers are programed.

The second major category of large-scale release of GEMs is in pollution abatement. For this purpose, microorganisms (again, mainly bacteria) are being designed to eliminate specific pollutants. In this use and in proposed agricultural uses, the public

concerns – as expressed both by current and proposed governmental regulation and by efforts of citizens' groups to ensure such regulation – focus on the potential for released microbial populations to escape control over their geographic distribution and their activities. The first such releases have revealed, however, that not only can released microbes be contained; they can be eliminated from the site of application when their employment is terminated (Lindow and Panopoulos, 1988).

A third category of use for genetically-engineered microorganisms and viruses is in the preparation of vaccines. At present, the "engineered" vaccine agents are predominantly for veterinary use, but vaccines for use in humans are being developed. Although no immunization procedure has employed an unmodified natural pathogen since Edward Jenner demonstrated in 1796 that cowpox virus (vaccinia) could be used to immunize humans against smallpox virus (variola), direct genetic manipulation of immunizing agents appears to be regarded as potentially more hazardous than traditional, empirical preparation of low-virulence or non-virulent agents. In practice, to engineer an agent genetically requires a more complete characterization of the agent than was required for previous means of developing immunogens. Nevertheless, more complete is not complete, and concerns about engineered agents are justifiable, if on no other basis than on the grounds that if genetic modification can be achieved in the laboratory, it might also occur in "nature," i.e., in the immunized population of livestock or humans.

Issues regarding the uses of genetically-engineered microorganisms and viruses were addressed by speakers in this AAAS symposium. As microbiologists participating in these developments, the speakers are concerned not only with the safety of the proposed uses of engineered microbes and viruses, but also with the efficacy of the newly-developed modified agents. The responsibility of scientists in contributing to technology includes evaluation of whether positive expectations are likely to be realized, as well as of potential hazard. In the case of the proposed uses of bacteria to reduce frost damage to crop plants, field studies conducted since the symposium in February 1987 have demonstrated that such protection is afforded by the bacteria, and that the methods employed to restrict their dispersal to the target crops are effective. These field tests were also of great value in assessing methods for monitoring dispersal of released GEMs and the influence on GEM persistence and dispersal of weather conditions, whose variability cannot be adequately evaluated in indoor tests (Seidler and Hern, 1988).

Assessment of potential hazards and of ecologic impact of GEMs released for agricultural and pollution abatement purposes is the goal of research in more than forty U.S. microbiological laboratories currently associated with the Risk Assessment Research Program of the U.S. Environmental Protection Agency. This program comprises projects to evaluate the interaction of GEMs with various natural communities (including indigenous microorganisms, and insects and other invertebrates) and geochemical processes, as well as on their potential influence on human and crop plant welfare. A major effort within the program is to conduct as much of this research as possible in confined simulated environments, and to proceed to outdoor experiments only when every conceivable influence has been tested as far as possible in settings such as greenhouses and water tanks.

Even when any particular release program proceeds to field studies, the scale of initial release will be small relative to proposed commercial and agricultural uses. At present, and probably for the next five years or so, only limited-scale tests are planned, and it is those tests that are the focus of current proposals for regulation (Office of Technology Assessment, 1988). The need for and focus of regulation for broader release programs cannot be meaningfully assessed until the small-scale tests are conducted and

analyzed. The research progresses reasonably from the laboratory to the simulated environment to the test plot to general use; so far, the scientists, the government agencies, and the commercial participants are pursuing that reasonable and responsible course, without short-cuts. Similarly, the entire gamut of potentially useful genetically-modified organisms is included in the contemplation of regulatory needs, plants and animals as well as microorganisms and viruses (Office of Technology Assessment, 1988; see Table 1.1 on page 100). It is highly probable that no previous technological addition to human activities has been so thoroughly examined and regulated *ab initio*, or the public so closely involved and fully informed as it is regarding the proposed introduction of the fruits of genetic engineering into agriculture and health care.

The extensive care regarding both efficacy and safety in the E.P.A.-associated risk assessment research is evident also in commercial and university research with GEMs, and is reflected in the considerations presented in this volume by Drs. Fischhoff and Watrud (on the use of microbial genes to protect crop plants against insect damage) and by Dr. Curtiss (on the use of modified pathogens and engineered vectors for immunization). The purpose of these presentations, as was the purpose of the symposium, is to display the depth and thoroughness of the considerations involved in the microbiological studies that are preparing for these uses of microorganisms and their genes, and to reassure non-microbiologists that the potential benefits are not being exaggerated, nor are the potential hazards being underestimated.

An entirely different kind of use of microorganisms is possible, *viz.*, intentional damage to agriculture or directly to human populations. Such use has come to be known as "Biological Weaponry," or "Biological Warfare." In 1970-71, U.S. microbiologists joined international microbiologists in urging that BW facilities be converted to peaceful uses (*ASM News*, 1970). The U.S. government, a signatory to the Biological Weapons Convention of 1972, claims to have done so. Nevertheless, the U.S. Army and, on a smaller scale, the U.S. Navy maintain significant research efforts in microbiology. Non-military microbiologists, as well as the general public, are curious about these research programs. Both communities are concerned that such programs may provide an offensive BW capability, despite the official position of the federal government and of the nation's society of professional microbiologists. The presentation by Dr. Chet Roberts of the U.S. Army Medical Research and Development Command describes the principal microbiological research programs currently conduct by that Command. His discussion illustrates the needs of the military for continuing microbiological research to support diagnosis, treatment and immunization against diseases to which troops are more likely to be exposed than is the civilian population. Dr. Roberts describes the BW research of the Command as defensive and directed entirely toward the development of diagnostic methods, therapeutic drugs and vaccines against potential BW agents. Dr. Roberts further points out that in addition to serving the welfare of U.S. troops, the activities of microbiologists in military research extend to health problems experienced by nations other than the U.S. Because of this, world health – not just that of U.S. armed forces – benefits from their studies.

Another aspect of the international impact of U.S. microbiological research is the testing and marketing of products in other nations. In some instances, testing or marketing abroad is necessary because the target health problem is minimal or non-existent in the U.S. In other instances, it may occur because such activities or products are not licensed for domestic use. At present, although exported products are subject to the same standards as those tested and marketed domestically, less vigilance is exercised by U.S. agencies over products sent abroad. There is, consequently, a greater burden of responsibility on individual microbiologists to attempt to ensure that the products to

which they contribute meet the standards for domestic applications, and that the use of those products is unquestionably "proper and beneficent" with respect to the nations to which they are distributed. As genetic technology accelerates, the attractiveness of non-U.S. sites for testing and marketing will increase and so will the need for regulatory and individual vigilance.

As implied by Dr. Curtiss' discussion, the current rush to litigation even before problems arise from technological advances in biology is not in all cases convincingly in the public interest. Despite the most conscientious care in the employment of microbes, instances of unanticipated and untoward consequences may occur, from or in purported fear of which some individuals will attempt to reap personal benefit in the form of material compensation or public attention. The consequences of such actions should be evaluated as rigorously as those of microbiologists' attempts to improve the length and quality of human life through microbiological research.

The overall intention of the symposium was to expose and examine the level of microbiologists' concerns regarding the consequences of the uses of microbes and their products. Formally, the nation's microbiologists have expressed a sense of responsibility to ensure that the public is accurately informed regarding the uses of microbiology, and that they themselves participate only in uses that benefit humans. In the past, microorganisms – a renewable, inexpensive natural resource – have been used to enrich our foods, increase agricultural productivity, decontaminate society's wastes, and treat and prevent infectious diseases through the production of antibiotics and the preparation of vaccines. The benefits derived from past and continuing uses of microbes and their products are incalculable, and the hazards have proved minimal and greatly outweighed by the benefits. It is hoped that the symposium demonstrated that enthusiasm for increased uses of microorganisms through expanding microbiological technology has increased, not decreased, the sense of responsibility of microbiologists regarding the impact of their professional activities on human welfare.

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Microbes as a Source of Genes for Agricultural Biotechnology

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The use of microbes or microbial products in agriculture has a long history. Biologically specific *Rhizobium* seed inoculants are used worldwide for legumes such as soybean, alfalfa and clover. One of the most widely used pesticidal microbes, *Bacillus thuringiensis (B.t.)*, has been used commercially as an insecticide for 20 years. In spite of these successful applications, microbes and microbial products are relatively underexploited in agriculture. Whereas thousands of natural products have been isolated from microbial species such as *Streptomyces*, and dozens of these are in use as pharmaceutical agents, in contrast, only a fraction of these compounds has been tested for agricultural use.

In the past several years, advances in genetic engineering and recombinant DNA technology have opened new possibilities for the agricultural use of microbes or their products. Genes can be isolated, characterized, and engineered for expression in heterologous host organisms. Because of these advances, it is now possible to view microorganisms as a vast, relatively untapped source of new genes and gene products of potential utility in agriculture.

Figure 1 illustrates the conceptual framework for these new applications. As illustrated, naturally-occurring microbes with agronomically useful traits are the starting material. The heterologous host organisms can be either other microbial species or higher plants. In this report we will focus on two applications involving the recruitment of the microbial gene encoding the insect control protein from *Bacillus thuringiensis* for expression in two heterologous hosts: a) plant colonizing *Pseudomonas fluorescens*, and b) tomato plants (*Lycopersicon esculentum*).

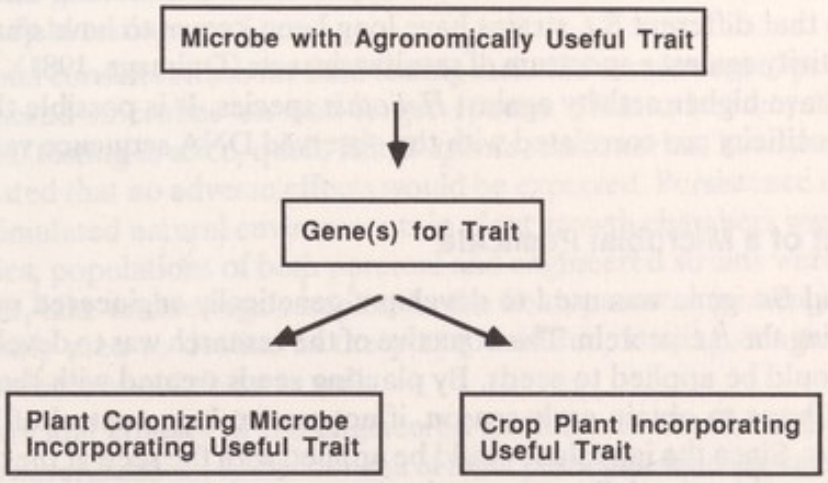

Figure 1. Conceptual scheme for genetically engineering plant colonizing microbes or crop plants with agronomically useful genes from microbial sources.

Bacillus thuringiensis

Bacillus thuringiensis is a naturally-occurring entomocidal bacterium. Upon sporulation, *B.t.* produces a parasporal protein crystal composed of subunits of one or a few protein species. These crystal protein subunits are the active insect control agents in *B.t.* (Aronson *et al.*, 1986). Most strains of *B.t.* are specifically active against lepidopteran insects (caterpillar larvae of moths and butterflies). More recently, strains have been described which have specificity for dipterans (mosquitoes and flies; Goldberg and Margalit, 1977) or coleopterans (beetles; Kreig *et al.*, 1983). Lepidopteran-specific *B.t.* strains have been utilized as commercial insecticides for many years (Bulla *et al.*, 1985). They have beneficial properties such as a high degree of insect specificity and a lack of activity against nontarget insects or higher organisms such as fish, birds and mammals, including man. On the other hand, typical *B.t.* preparations do not persist well after field application and so require frequent reapplication during the season. Also, they are not very active against soil-borne pests.

Scientists at Monsanto and elsewhere have been able to isolate the genes encoding lepidopteran-specific *B.t.* proteins. In our case, the gene was isolated from *B.t.* var. *kurstaki* HD-1, which is the strain found in Dipel®, a commercial *B.t.* preparation. This gene was cloned on plasmid vectors in *E. coli*, where it has been extensively analyzed (Watrud *et al.*, 1985; Fischhoff *et al.*, 1987). The gene encodes a protein of 1,156 amino acids that was expressed in *E. coli* in an active form. The DNA sequence of the gene has also been determined. The combination of expression of active protein in *E. coli* and the DNA sequence has allowed the introduction of defined changes into the gene and analysis of their effects on insecticidal activity. In particular, a variety of deletion variants of the gene were created in which sequences encoding either end of the protein or internal segments were removed. This deletion analysis has lead to the conclusion that only the N-terminal half of the protein is necessary for activity; the C-terminal half is dispensable. A similar conclusion has been reached for other lepidopteran active *B.t.* genes (Shibano *et al.*, 1985; Adang *et al.*, 1985; Schnepf and Whiteley, 1985; Hofte *et al.*, 1986; Wabiko *et al.*, 1986). Comparison of the DNA sequence of our gene to that of other *B.t.* genes has shown that the genes fall into a family of related members. Within the active N-terminal domain, the genes are composed of a highly-conserved region extending from the N-terminus for approximately 350 amino acids followed by a variable region, of which at least four versions have been observed, of approximately 250 amino acids. It is interesting to note that different *B.t.* strains have long been known to have quantitative differences in activity against a spectrum of sensitive insects (Dulmage, 1981). For example, some strains have higher activity against *Heliothis* species. It is possible that these differences in specificity are correlated with the observed DNA sequence variation.

Development of a Microbial Pesticide

The isolated *B.t.* gene was used to develop a genetically engineered microbial pesticide expressing the *B.t.* protein. The objective of the research was to develop microbial inocula that could be applied to seeds. By planting seeds treated with those microbes, farmers could hope to obtain early-season, if not season-long control of lepidopteran soil-borne pests. Since the inoculum would be applied with the seed at the time of planting, the farmer could potentially conserve the time, energy and extra cost of one or more insecticide applications. The same approach could also be applied to the development of a foliar inoculum that could have improved persistence properties compared to *B.t.* itself.

The other component of an engineered microbial pesticide is the host organism. Criteria for potential recipients of the *B.t.* gene were that they had to:

- be non-pathogenic,
- be plasmid-free, plasmid-cured or plasmid characterized,
- show limited acceptance of plasmids from other microbes,
- maintain and express the introduced trait, and
- have several known antibiotic sensitivities.

In addition, the organisms had to have the ability to colonize the roots of the target crop plants at high density. Several good root-colonizing isolates of *Pseudomonas fluorescens* were found that met these criteria.

Initially, the *B.t.* gene was introduced into these *P. fluorescens* strains simply by cloning the gene on a broad host range plasmid that was replicated in these hosts. As was the case with *E. coli*, the *B.t.* gene was found to be expressed in *Pseudomonas* at levels sufficient to kill lepidopteran larvae (Watrud *et al.*, 1985). A plasmid-borne *B.t.* gene was not considered appropriate for field use, however. For these purposes, it was desired to have the *B.t.* gene present as a stable chromosomal insert. The advantages of chromosomal insertion were felt to be minimization of the possibility of horizontal gene transfer in the environment and stability of expression.

The systems used to introduce the gene into the chromosome utilized a transposable DNA element, the well characterized Tn5 (Berg and Berg, 1983). Initially, the *B.t.* gene was inserted into the central region of a Tn5 element that was competent to transpose into the chromosome of *Pseudomonas*. Strains containing this inserted *B.t.* gene were again found to be active against lepidopterans (Obukowicz *et al.*, 1986a). Because Tn5 contains a transposase gene essential for movement of the element, the composite Tn5-*B.t.* element could potentially move to other sites in the chromosome or into plasmids which happened to enter the cell. Although the rate of transposition is quite low even when a functional transposase is present on Tn5, this rate can be reduced even further if the transposase gene is inactivated. Systems were successfully developed in which the *B.t.* gene was transferred into the *Pseudomonas* chromosome but was now embedded within Tn5 derivatives that did not encode functional transposase (Obukowicz *et al.*, 1986b, 1987). In such strains, the *B.t.* gene should be virtually as stable as any other chromosomal gene. It was these stable chromosomal insertions of *B.t.* that were considered for field testing.

Additional considerations for field testing included assessment of potential effects of the engineered microbes on non-target species (Watrud *et al.*, 1985). Extensive toxicological testing in mice, quail, fish, *Daphnia*, earthworms, honeybees and other insects indicated that no adverse effects would be expected. Persistence or survival of the strains in simulated natural environments in plant growth chambers was also studied. In those studies, populations of both parental and engineered strains were seen to decline in soil, river, lake and sewage samples. In the field, parental (nonengineered) isolates were similarly seen to decline as the plants matured, leading one to expect that engineered isolates would do so as well.

The pesticidal efficacy of the engineered microbes in the field has yet to be determined. However, laboratory evaluations of their pesticidal efficacy have been encouraging. The pesticidal host range of the engineered *Pseudomonas* root colonizers parallels that of *B.t.*; i.e., they show specificity for lepidopteran insects.

Genetic Engineering of Insect Tolerant Plants

In the past several years systems have been developed at Monsanto and elsewhere that allow the genetic engineering of plants (Fraley *et al.*, 1986). These systems are based on the plant pathogenic bacterium *Agrobacterium tumefaciens*, which causes crown gall disease. This disease is caused by the transfer of a segment of DNA (T-DNA) from the Ti plasmid of *Agrobacterium* into the chromosome of plant cells. The T-DNA encodes biosynthetic genes for phytohormones, and the expression of these genes in plant cells causes uncontrolled cell growth, or gall formation. The Ti plasmid contains other genes (*vir* genes) that are not transferred to the plant cell, but are essential for the transfer of T-DNA. Because the T-DNA genes themselves are not necessary for gene transfer, it has been possible to delete the phytohormone genes from the T-DNA while leaving the *vir* genes fully functional for gene transfer. These engineered strains of *Agrobacterium* are referred to as "disarmed."

Two other components are necessary for a functional plant genetic engineering system. First is the capability to engineer genes for expression in plant cells. This is especially important for genes derived from microbes because the signals for gene expression (promoters, transcriptional terminators, etc.) are completely different in procaryotic and eucaryotic organisms. Vectors for gene expression have been constructed at Monsanto that incorporate plant gene expression signals into cassettes into which genes of interest can be introduced. For example, one cassette that was utilized has the 35S promoter from cauliflower mosaic virus (CaMV) and the polyadenylation signal from the nopaline synthase gene of *Agrobacterium* (Sanders *et al.*, 1987) Between these control elements is a linker region composed of multiple restriction enzyme sites into which genes can be inserted. These cassette vectors are plasmids capable of replicating in *E. coli*, so that all of the recombinant DNA manipulations can be performed easily. After the vector is assembled, it is transferred by conjugation into *Agrobacterium* where, by homologous recombination, it integrates into the disarmed Ti plasmid and becomes a T-DNA capable of transfer to plant cells.

The other components necessary for plant genetic engineering are the capabilities to a) select for plant cells that have incorporated the new T-DNA, and b) regenerate whole plants from the selected cells. To achieve the first, the T-DNA also contains an antibiotic resistance gene (typically kanamycin resistance) which has also been engineered to function in plant cells (Fraley *et al.*, 1985). Thus, after *Agrobacterium* infection, the transformed cells can be selected by their ability to grow on tissue culture medium containing kanamycin. The ability to regenerate whole plants from tissue culture is highly species specific. Documented recovery of transformed plants following *Agrobacterium*-mediated gene transfer has now been reported for several dicotyledonous species. In many of these species, such as tobacco, tomato and petunia, the technology is now routine (Horsch *et al.*, 1985; McCormick *et al.*, 1986), and in several other important crop plants the technology is under active development. Genes transferred to the plant chromosomes by *Agrobacterium* are inherited in a Mendelian fashion and are expressed in the progeny (Horsch *et al.*, 1984).

Using the expression cassette system, the *B.t.* gene was engineered under the control of the CaMV 35S promoter. As described above, active truncated forms of the gene had been generated that encoded *B.t.* proteins consisting of the N-terminal 645 or 725 amino acids. These truncated *B.t.* genes were incorporated into plant transformation expression cassette vectors and transferred into *Agrobacterium*, which was then used to infect tomato explants. Following kanamycin selection, transformed tomato plants containing the *B.t.* gene were recovered (Fischhoff *et al.*, 1987). Tomato was chosen as the host plant

because it is easily transformable, it is an important crop plant, and it is susceptible to damage by several lepidopteran insect pests (Davidson and Lyon, 1987). For example, tobacco hornworm (*Manduca sexta*) can defoliate tomato plants leading to yield loss. Other pests such as tomato fruitworm (*Heliothis zea*) directly damage the tomato fruits, making them unmarketable. Both of these pests are sensitive to the action of the *B.t.* protein, but hornworm is more sensitive than fruitworm.

The engineered tomato plants were assayed for expression of the *B.t.* gene in two ways (Fischhoff *et al.*, 1987). First, Northern hybridization analysis was performed to detect mRNA from the *B.t.* gene. Full-length *B.t.* mRNA was detected, but was present at lower levels than expected. This obervation has also been made by others who have inserted similar *B.t.* genes into tobacco (Vaeck *et al.*, 1987). Second, the plants were tested for activity against lepidopteran insects. Insect assays were performed by exposing either excised leaves or whole plants to insect larvae. The insect bioassays showed that many of the transformed plants expressed the *B.t.* gene at levels sufficient to kill all of the applied hornworm larvae. When transformed plants that were toxic to hornworm were tested against fruitworm, it was possible to distinguish differences in level of expression. Some of the recovered plants were also highly active against fruitworm, killing all of the applied larvae. These bioassays demonstrate that the *B.t.* protein is expressed at levels sufficient to give insect control in spite of the lower than expected levels of mRNA.

During the summer of 1987, tomato plants expressing the *B.t.* gene were tested in the field. The plants were infested with egg masses of both hornworm and fruitworm. In the field, control, nonengineered plants that were exposed to hornworm larvae were completely defoliated. In contrast, the transformed plants suffered no agronomic damage. After infestation with fruitworm, there was a substantial decrease in the percent of tomato fruit showing damage on transformed plants compared to control plants. These results demonstrate that incorporation of the *B.t.* gene into plants is a technically feasible method of conferring insect control.

In addition to lepidopterans, other orders of insects such as coleopterans can be agronomically important pests. Recently, the gene encoding an insect control protein active against some coleopterans such as Colorado potato beetle has been isolated from *B.t.* var. *tenebrionis* (Sekar *et al.*, 1987; Hofte *et al.*, 1987; McPherson *et al.*, 1988). In the future, it should be possible to incorporate this gene into either plants or plant-colonizing microbes and test their potential for insect control.

Summary

Two approaches have been described here for the development of novel pest control agents based on biotechnology. In one case, a novel microbial pesticide was created by moving a single gene from an insecticidal bacterium (*B.t.*) into a plant-colonizing microbial host. This engineered microbe was active against lepidopterans and has the potential for increased efficacy compared to preparations of *B.t.* itself. In the second case, active truncated derivatives of the same gene were engineered and inserted into tomato plants. These transformed plants produced the *B.t.* protein and were tolerant to lepidopteran insects.

The examples described here have dealt with a single gene encoding a protein of known function. Other microbial products of potential agricultural value might be small metabolites synthesized by multi-step pathways encoded by multiple genes. Although isolation from microbes of multiple genes in a biosynthetic pathway is no doubt a larger task than single gene isolation, recent advances in *Streptomyces* gene cloning suggest that

this will be possible in some cases (Malpartida and Hopwood, 1984; Stanzak *et al.*, 1986). Proper engineering of multi-gene complexes for expression in heterologous microbial or plant genera is clearly a challenge for the future.

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Use of Genetically Engineered Microorganisms and Viruses as Vaccines

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A prime goal during the evolution of human society has been to improve practices to ward off and prevent disease. This objective has not only been directed at curtailment of human diseases but also diseases of the animals and plants upon which human society depends. The distinction between "organic" diseases afflicting a single individual and infectious diseases with the potential for contagious spread and epidemics was undoubtedly apparent before the time of recorded history. Thus, the practice of remaining aloof from and isolating "infected" individuals as first recorded for contending with those with leprosy undoubtedly became instinctive and a wise practice in dealing with a number of infectious diseases. However, avoidance proved to be impractical or even impossible for numerous infectious diseases. For example, variola virus, the causative agent of smallpox, is resistant to desiccaton, and therefore endemic and epidemic spread can be accomplished either by contact with infected individuals or from bedding, clothing, etc., which have been in contact with such individuals (White, 1925). Other infectious agents are disseminated by secondary hosts as is the case with plague due to rat-to-flea-to-human transmission of *Yersinia pestis* or of malaria which uses the mosquito as the purveyor (Mandell *et al.*, 1985).

The ultimate realization that poor sanitary conditions might augment the spread of infectious diseases undoubtedly contributed to improvements in personal hygiene and public sanitation. The discovery of insect vectors of infectious disease agents ultimately led to means to control these vectors either by preventing their reproduction, as by raising and lowering the water levels in TVA lakes, or by their extermination by potent insecticides such as DDT. In the future, insect vectors are likely to be better controlled by design of new biocides using recombinant DNA technologies and the genetic engineering of microbes and plants.

Today. we take for granted that prevention of an infectious disease is the most beneficial means of preserving good health and is also most cost effective. Thus, vaccination of children to prevent measles, tetanus, diphtheria, polio, etc., is an almost automatic practice during the first several years of life. The evolution of vaccination as a means to prevent disease has its own natural history and preceded any awareness of the nature of infectious disease agents or of the immune system.

The successful demonstration of vaccination to prevent smallpox by Edward Jenner in 1796 was preceded by more primitive means to "immunize" individuals. In China, powdered old crusts from smallpox victims were used for intra-nasal inoculation (Needham, 1970). Aging of the crusts was probably observed to result in attenuation and led to administering reasonably safe doses. It is evident that those subjected to this primitive means of vaccination (termed variolation) accepted and preferred the low risk of death due to variolation to the high risk of death if infected with smallpox! The practice moved

westward with modifications and improvements. In the early 18th century, variolation was introduced into Great Britain. By then, the old dried crusts were taken from individuals surviving a mild form of the disease (alastrim, with only 1% mortality) to reduce further development of infective disease (Timoni, 1714; Kahn, 1963).

In 1796, Edward Jenner used crusts from cowpox infections of cattle to immunize humans against smallpox. This procedure was based on his observations that milkmaids rarely contracted smallpox and on his reasoning that cowpox infection, which the milkmaids did contract, might preclude smallpox infection (Jenner, 1798; Dixon, 1962). Early practitioners using Jenner's vaccination protocol grew the cowpox in a variety of animal species and probably did so in combination with partially-attenuated strains of variola. The vaccinia virus used today to vaccinate people is thus distinctly different in DNA content from either cowpox or variola.

About 100 years later, Louis Pasteur commenced his pioneering work in preventive medicine. He initiated efforts to vaccinate both animals and humans against a variety of infectious disease agents and, in 1885, developed a successful method to vaccinate against rabies. Pasteur dried the spinal cords of rabies-infected rabbits for varying periods of time so the virus would lose its potency. This material was injected into individuals daily for a period of 15 days after which they gained immunity and did not contract the disease (Pasteur, 1885). Some time later a method was developed in which phenol was used to inactivate the virus to vaccinate individuals bitten by a rabid animal; and, still later, another inactivating agent, ß-propiolactone, was used to inactivate virus grown in embryonated duck eggs (Davis *et al.*, 1980). At present, rabies viruses are grown in human fibroblast cells to obtain a relatively pure vaccine that causes very few adverse side effects (Plotkin *et al.*, 1976).

In contrast to current adherence to strict standards for use of the scientific method and for ethical conduct of experiments with humans, early efforts to develop vaccination procedures relegated these standards secondary to achieving success in preventing dread diseases. Recently, Bernard Dixon (1986) began his commentary in *Biotechnology* by criticizing infectious disease workers and corporations with the capacity to develop and market vaccines for timidity in getting on with developing a vaccine against AIDS with the following statement:

> A non-medically qualified individual uses material of unknown composition and toxicity to treat patients, including a child, who may be suffering from a potentially fatal illness. The individual does not even try to obtain informed consent, but publishes patients' names and addresses to help publicize some astounding claims. Moreover, like fraudulent quacks the world over, the individual keeps details of the 'treatment' secret, so that its validity cannot be independently validated. Perhaps worst of all, this reckless person injects human beings with an extremely virulent micro-organism before conducting tests in animals. Some patients die and a close collaborator who is a medical doctor dissociates himself from his colleague's work.

These statements refer to Louis Pasteur's work in eradicating rabies by his vaccination protocol. Obviously, he eventually received great acclaim for taking risks far in excess of what would be acceptable today. In my opinion it is fortunate that he did.

The last vaccine to be discussed historically here illustrates several potential problems we face today. Initially, vaccination against polio depended on the killed Salk vaccine (Salk *et al.*, 1953), but use of live vaccines followed quickly. Three attenuated polio strains developed by Sabin are administered on sugar cubes or as a liquid (Sabin, 1957). We consume the attenuated viruses which colonize the intestinal tract and induce immunity. Attenuated Types I and II viruses are genetically stable and do not revert to a fully

virulent form. On the other hand, the Type III form can revert to regain virulence and about one out of every 3,000,000 individuals vaccinated with this virus contracts paralytic polio (Henderson *et al.*, 1964). Therefore, one of the concerns about attenuated vaccines – be they viral or bacterial – is their potential to revert to a fully virulent form and to cause disease. Another issue raised by use of the attenuated live polio virus vaccine has to do with dissemination and persistence of the vaccine agent. Very often, the idea of dissemination and persistence in the environment of genetically engineered microorganisms is feared and therefore engenders public opposition. In the case of the polio vaccine strains, this is, however, a desired end. Because the live vaccine strains colonizing the intestinal tracts of many of us are disseminated in the environment, many people who do not get vaccinated in a pediatrician's office become naturally immunized by consuming contaminated water (Salk, 1980).

Principles of Microbial Pathogenesis

Infectious disease is the product of a sequence of events. First, the microbial pathogen must gain entry into the host through a suitable portal. This could be by ingestion, inhalation, injection due to the bite of an insect vector, or wound infection. Second, most pathogens must locate and attach to a specific host receptor for the pathogen-host combination. Third, the pathogen must either multiply to colonize the specific host surface or invade through that surface to either become intracellular or multiply in some extracellular space within the body. Fourth, the pathogen must then synthesize products (e.g., enzymes, toxins, acid, etc.) that act to overcome the host or to destroy host tissues.

The genetic control and specification for this sequence of events have evolved for each pathogen-host combination and undoubtedly are very sophisticated. Expression of colonization and virulence determinants is temporally regulated for some pathogens in response to the environment and/or to the host. For example, *Shigella* species do not express their colonization and virulence properties until they come in contact with their warm-blooded host (Maurelli *et al.*, 1984). Thus, they do not synthesize proteins needed for colonization and virulence at the ambient temperatures of contaminated water but only after being swallowed by the human target. It also appears that many pathogens have multiple means to accomplish their feats, making it even more difficult to devise ways to prevent such infections. Nevertheless, if the mechanism(s) by which a pathogen colonizes, invades, or overcomes host defenses can be established in detailed biochemical terms, it should be possible to use that information to develop a vaccine for the prevention of infection and disease.

Infectious Diseases

Worldwide, infectious diseases constitute a tremendous personal and economic loss. In the United States, a very considerable proportion of office visits to physicians is to contend with infectious disease agents or for immunization to prevent these diseases. In the developing world, perpetual diarrheal disease exacerbates the problems of food shortages and poor diet resulting in severe malnutrition (Gordon and Scrimshaw, 1970). This is particularly devastating when the consequences occur *in utero* and during early childhood to retard brain development. Parasitic diseases afflicting many individuals throughout life (Mandell *et al.*, 1985) guarantee that these societies are relegated to a dismal status without much hope of betterment. It has, therefore, been a goal of microbiologists since the time of Jenner to develop strategies that would prevent infectious diseases. To establish the biochemical basis for colonization and virulence, scien-

tists take a multidisciplinary approach using genetics, biochemistry, immunology, and animal research. For example, if one is interested in knowing whether a particular entity of the infectious agent is essential for virulence, mutation is used to eliminate the ability of the agent to produce that attribute. The resultant mutant is then evaluated for its potential to cause disease in the appropriate animal host. The corollary approach is to purify the putative virulence antigen and immunize the appropriate animal host with it to determine whether the animal becomes immune and does not contract disease when challenged with the pathogen. Gene cloning (Maniatis *et al.*, 1982) and the techniques of molecular genetics (Davis *et al.*, 1980; Silhavy *et al.*, 1984) are invaluable for these types of analyses of microbial pathogenicity.

Immunity and Immunization

There are three types of immunity: mucosal or secretory, humoral, and cellular. Little is stated about mucosal or secretory immunity in most textbooks on immunology since means to enlist this branch of the immune system in fighting disease have been developed only recently. Mucosal immunity is due to production of an antibody termed secretory IgA (sIgA) by secretory tissues in the body (McCaughan and Basten, 1983; McGhee and Mastecky, 1983; LeFever *et al.*, 1984; and Mestecky, 1987). sIgA can block attachment and colonization of pathogens on a mucosal surface and also can inhibit invasion of pathogens through a mucosal surface bathed with sIgA against those surface antigens of the pathogen required for such invasion (McNabb anf Tomasi, 1981). Mucosal immunity is therefore important in diminishing infectious diseases by all pathogens that colonize or invade through a mucosal surface.

Humoral immunity is familiar to most and is due to IgM and IgG antibodies in the blood (Davis *et al.*, 1980; Hood *et al.*, 1984). These antibodies neutralize toxins (Pappenheimer and Gill, 1973), facilitate phagocytosis, and complement-mediated cytotoxicity (Davis *et al.*, 1980; Hood *et al.*, 1984), both of which lead to the death of the invading microorganism or, in the case of viruses, neutralize the virus (Davis *et al.*, 1980; Hood *et al.*, 1984) to prevent infection and multiplication inside cells. Humoral immunity is therefore important in controlling those infectious diseases due to release of systemically distributed toxins and infectious diseases where the organism invades and multiplies in the blood or in extracellular spaces within the body. Humoral immunity is also an important means of defense against viral infections.

Cellular immunity is of two types. One is termed a delayed-type hypersensitivity response which causes T lymphocytes to stimulate macrophages to kill bacterial, protozoan, and mycotic pathogens. In the other type, cytotoxic T lymphocytes are directed to kill host cells infected with viruses (Davis *et al.*, 1980; Hood *et al.*, 1984). Cellular immunity is therefore critically important in resolving infections with bacterial and protozoan intracellular parasites and viruses.

Individuals who survive natural infection with some infectious disease agent usually acquire lifelong immunity against future infection with that pathogen. Of course, no one likes to acquire immunity that way because there is some chance of adverse consequences, including death. Vaccination methods have thus been developed and tested as a preferable means for inducing immunity to the disease agent or to its by-products. Use of toxoids (inactivated forms of toxin) for immunization by injection to elicit a humoral immune response has been effective in precluding the serious consequences of systemic toxemia associated with diphtheria and tetanus (Pappenheimer and Gill, 1973; Davis *et al.*, 1980; and Hood *et al.*, 1984). On the other hand, similar strategies have not been ef-

fective for preventing the consequences of *Vibrio cholerae* infection (Finkelstein, 1984), since the toxin is active only locally in the cells of the small intestine and not systemically. Thus, a humoral immune response against cholera toxoid is of little or no benefit.

Parenteral immunization with purified components of viral and bacterial pathogens has given promising results in experimental animal systems (Robbins *et al.*, 1982; Brown, 1984; Finkelstein, 1984; Germanier, 1984; and Brown *et al.*, 1986), but, with the possible exception of vaccination against hepatitis, few subunit vaccines are currently being used. Quite possibly the expense of subunit vaccines acts to discourage their development.

Killed viruses and bacteria have been used as vaccines for quite some time. Injection of killed vaccines induces humoral immunity, but seldom gives long-lasting protection, thus necessitating periodic booster immunizations (Robbins *et al.*, 1982; Brown, 1984; Finkelstein, 1984; Germanier, 1984; and Brown *et al.*, 1986). In addition. some killed vaccines have more frequent adverse side effects associated with their use than is desirable (Robbins *et al.*, 1982; Brown, 1984; Finkelstein, 1984; Germanier, 1984; and Brown *et al.*, 1986).

Live attenuated bacteria or viruses used for immunization do, however, induce long-lasting immunity, sometimes for the life of the immunized individual (Germanier and Furer, 1971; Germanier and Furer, 1975; Hoiseth and Stocker, 1981; Machett *et al.*, 1984; Paoletti *et al.*, 1984; and Brown *et al.*, 1986). Also, live vaccines are less expensive to prepare and to administer than are subunit and killed vaccines. One potential problem with a live vaccine is the possibility of reversion so that the attribute altered to attenuate the live vaccine strain is now able to exhibit its wild-type properties, resulting in virulence and thus disease. Another potential problem is that the vaccine strain might be disseminated and persist in the environment with the remote possibility for gene transfer and/or recombination with other microbes.

New Antiviral Vaccines

Recombinant DNA techniques have been used to develop two different types of antiviral vaccines. In the first, molecular genetic procedures are used to render a virus avirulent by deleting genetic information without impairing the ability to elicit an immune response. In the second, avirulent virus mutants are engineered to express genes for important virulence attributes of other viruses to result in bivalent or multivalent recombinant vaccines that elicit immunity to two or more viral diseases.

The first step in developing an anti-viral vaccine is to determine which viral genes can be deleted or altered to eliminate the disease-causing potential without impairing immunogenicity. As stated above, isolation and characterization of mutants for virulence constitutes the first step in this process. Gene cloning could then be employed to define more rigorously, in biochemical and molecular terms, the limits of the gene and the nature of its protein product. Using this information, the gene in question can be deleted from the virus genome or, where an altered gene product is desired, a mutant form of the gene substituted for the wild-type allele. These live vaccine candidates can then be evaluated for loss of virulence, retention of immunogenicity, and safety. It should be emphasized that these methods for attenuating viruses are exceedingly precise since the exact nucleotide sequences eliminated or altered can be determined. The likelihood for reversion to a virulent form is thereby all but eliminated, and one can have considerable confidence in both the efficacy and the safety of the vaccine.

Pseudorabies is a disease of swine caused by a herpes virus (Leman, 1981). Like herpes viruses in humans, this herpes virus has the potential to exist in a latent form that can

be activated to cause severe disease under conditions still poorly understood, and pseudorabies results in considerable financial loss in the swine industry. Kit and colleagues (1985) were first to use mutant analysis and, eventually, gene splicing technology to delete from the pseudorabies virus the gene for thymidylate kinase. This deletion (Δ) mutation diminishes the ability of the virus to multiply in many host tissues and to cause viremia. The use of this Δ*tk* mutant, and derivatives of it, as a vaccine appears to induce a high level of immunity to infection with the wild-type pseudorabies virus (Kit *et al.*, 1986; Kit *et al.*, 1987). Presumably, similar strategies will be used to develop avirulent deletion mutants of other viruses that retain immunogenicity and will thus be effective in immunizing against a number of viral diseases, especially of agriculturally important animals.

Development of bi- and multivalent recombinant vaccines has made use of similar approaches except that gene sequences are added rather than deleted. The most promising results to date have come from experiments with genetically modified vaccinia virus, the virus first employed for vaccination as developed by Edward Jenner over 200 years ago. Since vaccinia is already avirulent and yet immunogenic, one must only devise strategies for introducing genetic information, encoding some important attributes from other viruses, and expressing this information by the recombinant vaccinia virus. The procedures for accomplishing this have been worked out by Moss and colleagues (Machett *et al.*, 1984; Moss and Flexner, 1987) and Paoletti and co-workers (1984). These involve a multi-step process as depicted in Figure 1. Gene cloning and recombinant DNA technology are employed to insert a gene from a foreign virus into the vaccinia *tk* gene contained in a plasmid capable of replicating in *Escherichia coli*. This recombinant plasmid is simultaneously introduced into a mammalian cell upon infection with vaccinia. Allele replacement of the wild-type *tk* gene with the insertionally inactivated *tk* gene containing the inserted foreign viral gene sequence can be selected easily because tk^+ viruses are able to incorporate the analog 5-bromodeoxyuridine into the DNA (which is ultimately lethal) while *tk*- mutants are unable to do so. The recombinant vaccinia virus can then be plaque-purified, stocks prepared, and the virus tested for ability to induce an immune response against the product specified by the foreign viral gene inserted into the vaccinia *tk* gene.

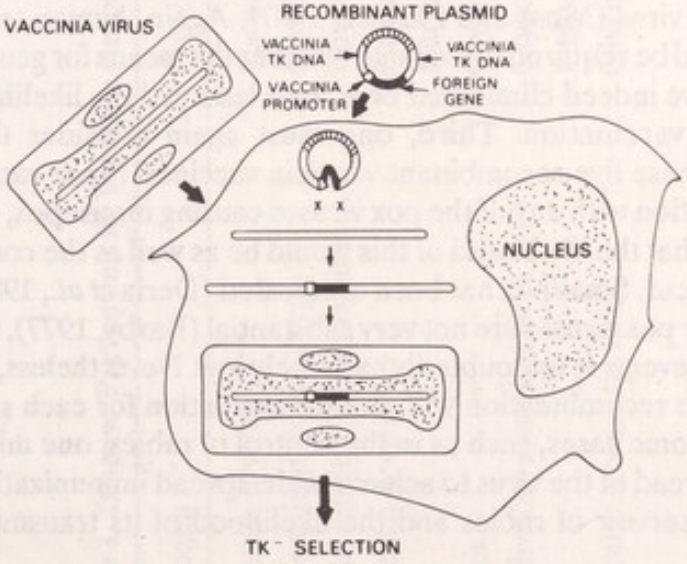

Figure 1. Formation of Vaccinia Virus Recombinants

As enumerated in Table 1, an increasing number of recombinant vaccinia vaccine strains have been constructed and shown not only to elicit an antibody response against such viral agents as hepatitis B, herpes simplex Type I, influenza, rabies, etc., but also shown to induce protective immunity against the viral diseases caused by those viruses in experimental animals including chimpanzees, mice, and rabbits (Moss and Flexner, 1987).

The advantages of using recombinant vaccinia viruses for vaccination are many-fold (Moss and Flexner, 1987). First, these recombinant vaccinia vaccines elicit cell-mediated as well as humoral immunity. Second, since the vaccinia virus genome is linear, it is possible to insert multiple genes from a variety of viral pathogens and thus develop multivalent vaccines. Third, the methods for propagating the vaccine strains are simple, well established, and economical; in large part because of all the experience with using vaccinia for immunization against smallpox. Fourth, the vaccine can be freeze dried. It is then reasonably thermostable and has a long shelf life. Fifth, the vaccine is easy to administer by employing the same method used for vaccination with vaccinia, namely, distribution of the viral vaccine on the skin surface and then repeated puncturing with a bifurcated needle. Sixth, vaccinia has a wide host range and thus is not only useful for immunizing humans against viral diseases, but also has many veterinary applications in immunizing agriculturally important animals.

There are, however, some potential disadvantages that must be considered. First, many members of the adult population who were immunized with vaccinia virus may possess residual immunity and thereby be refractory to immunization with recombinant vaccinia viruses. Animal experimentation should provide information to assess the severity of this problem, although human trials will be necessary to determine the magnitude of the problem in the human population. A related problem is whether different vaccinia vaccines can be administered successively with equal effectiveness in inducing immunity to different expressed colonization or virulence antigens. If not, it will be necessary to construct several different viral vectors with different surface attributes to circumvent this problem. Second, vaccination with vaccinia is associated with infrequent, but serious, complications (Fenner *et al.*, 1974; Mandell *et al.*, 1985). In this regard, it appears that the *tk* vaccinia strains are associated with fewer adverse consequences in immunization trials with animals than are encountered when vaccination is with the wild-type vaccinia virus (Moss and Flexner, 1987). Again, human trials on a relatively massive scale would be required to evaluate whether the means for generating the recombinant vaccinia have indeed eliminated or at least lessened the likelihood of adverse sequelae following vaccination. Third, one must again consider the environmental consequences of these live recombinant vaccinia vaccines. Since vaccinia can undergo genetic recombination with any of the pox viruses causing mousepox, cowpox, smallpox, etc., one can ask what the likelihood of this would be as well as the consequences if such an event should occur. Smallpox has been eradicated (Deria *et al.*, 1980) and the animal reservoirs for other pox viruses are not very substantial (Baxby, 1977), thus the likelihood for recombination events is undoubtedly extremely low. Nevertheless, the consequences of such improbable recombination will require evaluation for each specific type of live vaccine strain. In some cases, such as in the control of rabies, one might even want dissemination and spread of the virus to achieve wide-spread immunization of wild animals to diminish the reservoir of rabies and the likelihood of its transmission to domestic animal species.

Table 1. Disease Prevention by Vaccinia Recombinants

Pathogen	Protein Expressed	Syndrome Prevented	Species Protected
Hepatitis B virus	Surface antigen	Hepatitis	Chimpanzee
Herpes simplex virus type 1	Glycoprotein D	Lethal and latent infection	Mouse
Friend murine leukemia virus	Envelope protein	Leukemia	Mouse
Influenza A virus	Hemagglutinin	Lower resp. infection	Mouse
	Nucleo protein	Lethal infection (partial)	Mouse
Rabies	Glycoprotein	Encephalitis	Mouse, rabbit, fox
Respiratory syncytial virus	Glycoprotein	Lower resp. infection	Cotton rats
	Fusion protein	Lower resp. infection	Cotton rats
Vesicular stomatitis virus	Glycoprotein	Lingual infection	Cow

New Bacterial Vaccines

The live avirulent recombinant or nonrecombinant viral vaccines described above elicit humoral and cellular immune responses. Although aerosolization or ingestion of viral vaccines has the potential to elicit a local immune response, there probably is a greater potential for eliciting mucosal immunity in addition to humoral and cellular immunity by using live avirulent bacterial vaccines. The development of live oral bacterial vaccine strains for immunization to elicit secretory, humoral, and cellular immune responses depends upon at least four types of discoveries. First, antigen delivery to the gut-associated lymphoid tissue (GALT or Peyer's patches) leads to a generalized secretory immune response (Cebra *et al.*, 1976; Bienstock *et al.*, 1978; McCaughan and Basten, 1983; McGhee and Mestecky, 1983; LeFever and Joel, 1984; and Mestecky, 1987). Second, orally-administered *Salmonella typhimurium* initially attach to, invade, and persist in the GALT before colonizing the liver and spleen in mice (Carter and Collins, 1974). Presumably, other *Salmonella* species causing invasive disease in other animal hosts have similar ports of entry. Third, enteric bacteria can be attenuated by mutation (Bacon *et al.*, 1950, 1951; Germainer and Furer, 1971; Germanier and Furer, 1975; Hoiseth and Stocker, 1981; Curtiss, 1986; and Curtiss and Kelly, 1987) to prevent disease without inhibiting their initial tissue tropism (Curtiss *et al.*, 1987b; Curtiss and Kelly, 1987). Lastly, essential colonization and virulence antigens have been defined for a number of microbial pathogens by a diversity of molecular genetic techniques (Macrina, 1984; Goebel, 1985).

Figure 2 depicts the mucosal immune network. There are eight to ten well-defined Peyer's patches in the small intestines of mice whereas in humans the Peyer's patches are much more numerous, but smaller. Each Peyer's patch possesses membranous microfold cells (M cells) overlying the surface of the lymphoid tissue underneath (Bye *et al.*, 1984). There are no goblet cells and therefore little or no mucin or glycocalyx covering Peyer's patches. The M cells serve to sample the contents of the intestinal lumen and convey antigens to antigen presenting cells that activate T lymphocytes which, in turn, activate B lymphocytes (Mestecky, 1987). These proliferate and migrate to the mesenteric lymph nodes and ultimately reach the peripheral circulatory system. These peripheral B lymphocytes are programmed to produce IgA and colonize all the secretory tissues of the body, including the lamina propria of the pulmonary, gastrointestinal, and genitourinary tracts, and all of the secretory glands (lacrimal, salivary, and mammary). There, the lymphocytes undergo final maturation to IgA-secreting plasma cells with the IgA being transferred to secretory epithelial cells that add secretory component(s) and release sIgA into the secretions.

Bacon and colleagues (1950; 1951) were first to investigate the avirulence of auxotrophic mutants of *S. typhi* and noted that mutants with requirements for purines, *p*-aminobenzoic acid (*p*ABA), and aspartate had reduced virulence for mice. Germanier and Furer (1971) demonstrated that *ga1E* mutants of *S. typhimurium* were avirulent and immunogenic in mice, and they constructed the *S. typhi ga1E* mutant Ty21a as a vaccine against typhoid fever in humans (1975). Hoiseth and Stocker (1981) devised strategies to generate deletion mutants lacking a gene (Δ *aroA*) specifying an enzyme early in the biosynthesis of the aromatic amino acid family of compounds, including *p*ABA which is needed for folate biosynthesis and dihydroxybenzoic acid, precursor to enterochelin needed for iron transport. We (Curtiss, 1986; Curtiss *et al.*, 1987b) have isolated and evaluated deletion mutants (Δ *asd*) lacking the enzyme aspartic ß-semialdehyde dehydrogenase, thereby imposing a requirement for diaminopimelic acid (DAP), an

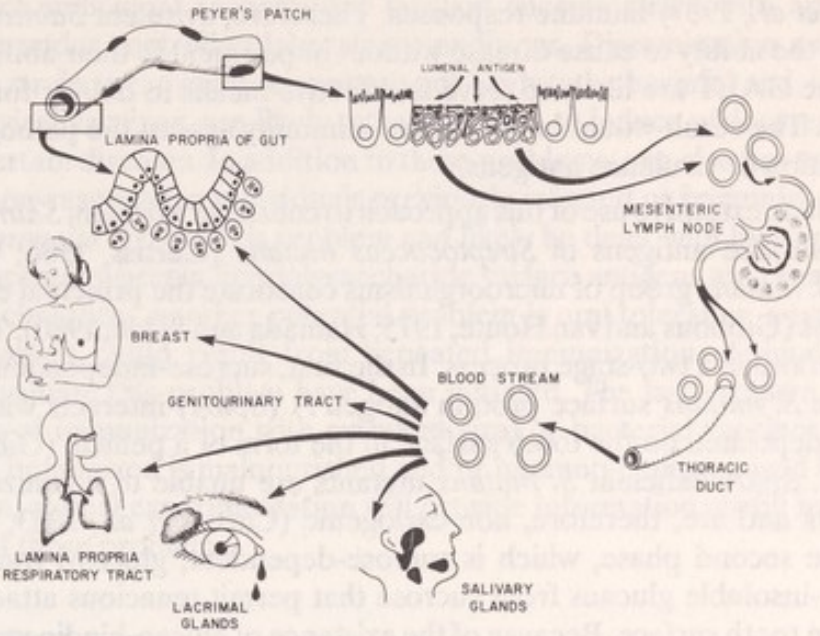

Figure 2. The Mucosal Immune Network Peyer's Patch

essential constituent of the rigid layer of the cell wall, and the enzyme thymidylate synthase,which is necessary to synthesize thymidine, an essential component of DNA. More recently, we (Curtiss and Kelly, 1987) have studied mutants unable to synthesize cyclic AMP due to a mutation in the gene for adenylate cyclase (*cya*) and the cyclic AMP receptor protein due to a mutation in the *crp* gene. *Cya* and *crp* mutants are thereby diminished in their ability to transport and metabolize carbohydrates and amino acids (Pasten and Adnya, 1976). All of these mutant strains are avirulent and have the potential to induce varying degrees of immunity. Reversion to the wild-type state resulting in virulence, a problem with the mutants isolated by Bacon *et al.,* (1950, 1951), is not a problem when employing deletion mutants generated by transposon mutagenesis as employed by Hoiseth and Stocker (1981) and by us (Curtiss, 1986; Curtiss *et al.*, 1987b; and Curtiss and Kelly, 1987). Supply of the required nutrient, either by the diet or the host, is a problem with some mutants (Δ *aroA*), but not with others (Δ *asd,* Δ *cya,* Δ *crp*). Some mutants, e.g., *ga1E*, have a tendency to accumulate secondary mutations that can render the strains non-immunogenic although retaining complete avirulence (Germanier and Furer, 1971). The Δ *asd* mutants are totally avirulent and although, like other avirulent *Salmonella* mutants, they home to the Peyer's patches, they do not persist long enough to induce humoral and especially cellular immune responses (Curtiss *et al.*, 1987b). The Δ *cya* Δ *crp* double mutants therefore seem to be the most satisfactory because of their genetic stability for both avirulence and immunogenicity (Curtiss and Kelly, 1987).

Several groups have used avirulent *Salmonella* to express colonization and/or virulence antigens specified by genes from other enteric pathogens using classical (Formal *et al.*, 1981), as well as recombinant DNA (Stevenson and Manning, 1985; Clements *et al.*, 1986; Maskell *et al.*, 1986; Curtiss *et al.*, 1987b; and Maskell *et al.*, 1987), means of gene transfer. Such studies have revealed that use of these live bivalent *Salmonella* vaccine strains elicits generalized secretory (Formal *et al.*, 1981; Stevenson and Manning, 1985; Clements *et al.*, 1986; Maskell *et al.*, 1986; and Curtiss *et al.*, 1987b; Maskell *et al.*,

1987), humoral (Brown *et al.*, 1987; Curtiss *et al.*, 1987b; Maskell *et al.*, 1987), and cellular (Brown *et al.*, 1987) immune responses. Therefore, avirulent *Salmonella* mutants that have lost the ability to cause disease without impairment in their ability to attach to and invade the GALT are likely to serve as effective means to deliver foreign antigens to the GALT. The result would be protective immunity against the pathogen supplying such colonization or virulence antigens.

We have made extensive use of this approach to construct avirulent *Salmonella* strains synthesizing surface antigens of *Streptococcus mutans* (Curtiss, 1986; Curtiss *et al.*, 1987b). The *S. mutans* group of microorganisms constitute the principal etiologic agent of dental caries (Gibbons and van Houte, 1975; Hamada and Slade, 1980). The organisms attach to the tooth in a two-stage process. In the first, sucrose-independent phase, it appears that the *S. mutans* surface protein antigen A (SpaA) interacts with the salivary glycoprotein deposited on the tooth surface in the form of a pellicle (Gibbons and van Houte, 1980). SpaA-deficient *S. mutans* mutants are unable to colonize the teeth of germ-free rats and are, therefore, non-cariogenic (Curtiss *et al.*, 1983; Curtiss *et al.*, 1987a). In the second phase, which is sucrose-dependent, glucosyl transferases synthesize water-insoluble glucans from sucrose that permit tenacious attachment of the microbe to the tooth surface. Because of the existence of glucan-binding proteins on the *S. mutans* surface, glucans also facilitate cell-cell interaction and plaque formation. Mutants lacking some glucosyl transferases are likewise unable to induce significant levels of caries (Michalek *et al.*, 1975). Construction of recombinant avirulent *Salmonella* strains expressing the SpaA and GtfA proteins has been achieved, and the feeding of these strains to mice elicits sIgA response against *S. mutans* in saliva and IgG responses in serum (Curtiss *et al.*, 1987b).

The advantages of using avirulent bivalent Salmonella vaccine strains are as follows. First, avirulent *S. typhimurium* derivatives can be constructed with different mutations that define their period of survival and multiplication in the GALT and spleen and so regulate whether and to what level they induce secretory, humoral, and cellular immunity. Second, the mutations responsible for these attributes can be transferred to other *Salmonella* species which have specificities for unique animal hosts. Third, oral administration of live recombinant avirulent *S. typhimurium* strains expressing colonization and virulence protein antigens can induce secretory, humoral, and cellular immune responses against the pathogen supplying the genes for the colonization and/or virulence antigens. Fourth, since many bacterial, viral, and fungal pathogens colonize or invade through a mucosal surface, effective secretory immunity would be an important first-line of defense and would reduce contagious spread of infectious diseases caused by those pathogens. Thus, recombinant avirulent bacterial vaccine strains may have a distinct advantage over recombinant viral vaccines for immunizing against those microbial pathogens in which mucosal immunity would be an important means of defense. Lastly, oral live bacterial vaccines are inexpensive to produce and administer.

The disadvantages of using avirulent *Salmonella* vaccine strains relate again to the issues of safety, loss of the avirulence attribute, and dissemination into the environment. Since the most recently developed *Salmonella* constructs employ two or more deletion mutations, either of which confers avirulence, there is little likelihood for restoration of any one or especially all of the missing genetic information by gene transfer with other microbes in the environment. Based on risk assessment experiments done at the height of the recombinant DNA debate in the 1970's, it can be estimated that such events would be at such low frequency as to be unmeasurable (Curtiss *et al.*, 1977). In spite of the difficulty in quantifying the probability for restoration of all the avirulence traits to virulence, it is fitting to ask what the consequence would be if such an improbable se-

quence of events should occur. The answer to this question, obviously, has to be determined for each individual recombinant bivalent vaccine strain with appropriate experimentation under controlled laboratory conditions. Dissemination and persistence of the vaccine strain in the environment are not likely to be harmful and, in fact, as with live avirulent viral vaccines, are likely to be desirable to induce widespread immunization against certain diseases. In addition to these problems, one also has to contend with the possible non-response in individuals previously infected or immunized with the immunizing *Salmonella* strain. This problem can likely be dealt with by using multivalent *Salmonella* vaccines wherein lipopolysaccharide surface antigens are changed by standard genetic techniques. Another potential problem is oral tolerance, a type of immune suppression which could result from repeated immunization. Animal experiments designed to evaluate this problem have been initiated. The last problem concerns the consequences of immunization with avirulent viral or bacterial vaccines when the individual to be immunized is malnourished and/or immuno-compromised by heredity or disease. Again, animal experimentation will provide information useful in assessing the significance of these problems.

Concluding Comments

The goal of successful immunization is to protect humans and animals from infectious diseases by diminishing the populations of various pathogens in the biosphere. Since we have already decreed that pathogens are to be oppressed, I trust that no one will defend their fate if modern technology is successful in bringing about extinction. Although this seems unlikely, there are some attributes of the human species – especially in the United States – which are likely to slow the rate of progress in attacking microbial pathogens. The propensity of some members of our society who have the misfortune of having an adverse experience to reap remuneration in excess of just compensation has led to a reluctance on the part of the pharmaceutical and biotechnology industries to jeopardize their net worths by risking liability losses associated with the introduction of new vaccines. Possibly, legislation will be enacted and implemented to provide indemnification to health care providers against liability claims in excess of justifiable needs. In the absence of such, it is likely that the health of farm animals and of those individuals in the developing world will benefit more rapidly than will those individuals in the supposedly more civilized societies.

Because of the likely widespread use of live vaccine strategies with both viral and bacterial vaccines in developing countries, we are likely to encounter consequences which will be applauded in one sense but may be associated with other difficulties. Thus, the improved nutrition and health of individuals in developing countries will lead to decreased infant mortality and optimal development of the central nervous system, resulting in a more productive, creative, and increased lifespan. In the short term, a major ramification will be a more rapid rate of population growth, which will have to be dealt with. If not, the consequences will be increased competition for land, depletion of natural resources, increased pollution and alteration of the atmosphere and environment. As an optimist, I have considerable faith that the same technological ingenuity which will deal with infectious diseases will, in the hands of others, contribute to contending with these other commanding worldwide problems.

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Microbiologists in Military Research

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Two questions most frequently asked of military microbiologists are: Where are the microbiologists in military research? What are they doing? The goals of this paper are to answer these questions and address ancillary issues that may be of interest to those concerned about responsible uses of microorganisms.

Most microbiologists engaged in military research are members of the U.S. Army Medical Research and Development Command (USAMRDC). This Command has nine major laboratories in the continental United States and five overseas laboratories. Within the United States, almost all of the microbiologists work at the Walter Reed Army Institute of Research (WRAIR) in Washington, D.C., or at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Ft. Detrick, Maryland. Overseas, most of the microbiologists are located at the Armed Forces Research Institute of the Medical Sciences (AFRIMS) in Bangkok, Thailand. The next largest grouping of microbiologists is at the Naval Medical Research Institute (NMRI) in Bethesda, Maryland, adjacent to the Uniformed Services University of the Health Sciences, where another group of microbiologists is active in research. Other microbiologists are engaged in clinical research at some of the military medical centers around the country. Finally, there are one or two microbiologists located at the Armed Forces Medical Intelligence Center (AFMIC), at the Chemical Research, Development, and Engineering Command (CRDEC), and at Dugway Proving Ground (DPG).

A complete discussion of what every microbiologist is doing would not be possible within the space and time allotted. Since the majority of microbiologists work within USAMRDC, this description will concentrate on research programs in the medical arena managed by USAMRDC. Its principal component is the Military Disease Hazards Research Program, which consists of basic and applied studies related either to medical defense against worldwide, naturally-occurring infectious diseases, or to medical defense against potential biological warfare (BW) agents. In addition, a separate program has been recently created to address medical protection against retroviruses such as the Human Immunodeficiency Virus (HIV).

Research on naturally-occurring infectious disease focuses primarily on prevention and, to a lesser extent, on treatment and diagnosis of those infectious diseases which would seriously hamper military operations. The impact of infectious diseases on military forces is well documented as the major cause of casualties in all wars in history (Table 1). Diseases of principal research interest are: malaria, diarrheal diseases, dengue fever, and hepatitis A. Other diseases of interest include leishmaniasis, schistosomiasis, trypanosomiasis, opportunistic infections (e.g., *Pseudomonas aeruginosa* and *Escherichia coli*), gonorrhea, meningococcal infections, Non-A and Non-B hepatitis, scrub typhus, epidemic typhus, and arboviral infections (Table 2).

The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

Table 1. Causes of Admission of Troops to Medical Units

Conflict	Battle	Non-Battle	
		Disease	Other
World War II	3.6%	85.7%	10.7%
Korea	17.3%	65.8%	16.9%
Vietnam	15.6%	70.6%	13.8%

Table 2. Recent Military Experience of and Defense Against Infectious Diseases

A. Experience:

Region	Diseases
Lebanon	Hepatitis A
Egypt; Thailand	Shigellosis
Grenada	Strongyloides; Hookworm
U.S., Europe, Far East	Gonorrhea; AIDS
Philippines	Dengue; Japanese Encephalitis
Panama	Leishmaniasis; Leptospirosis
Korea	Hemorrhagic Fever

B. Products Developed:

Typhoid Vaccine
Meningitis Type A, Type C, Type Y, Type W135 Vaccines
Adenovirus Vaccine
Mefloquine (antimalarial drug)
Pesticide Aerosol Generator
Back-Pack Pesticide Sprayer

Microbiologists are working in collaboration with other scientists to develop preventative measures against these diseases. Research directed towards controlling diseases involves the development of drugs and vaccines, as well as rapid identification and vector control. These studies include the identification or design of prophylactic and therapeutic drugs, investigation of their mode of action, and research on mechanisms of drug resistance. Involved with this are basic studies on organism pathogenesis and immune mechanisms so that potential targets for therapy may be discovered. Collection and analysis of epidemiological data, such as incidence, vectors, reservoirs, and bionomics which would aid in control of relevant infectious diseases are also important aspects of the activities of microbiologists in this program. Finally, basic animal and human studies applicable to the development of vaccines and drugs are conducted to assess their purity, safety, immunogenicity, and efficacy. All such studies are conducted in accordance with the guidelines of Federal regulatory agencies such as the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). In addition, guidelines of other organizations such as the American Association for Accreditation of Laboratory Animal Care (AAALAC) are followed.

Policy Decisions Regarding U.S. Biological Warfare Research

National Security Decision 35 (25 November 1969)

The U.S. shall renounce the use of lethal biological agents and weapons, and all other methods of biological warfare. The U.S. will confine its biological research to defensive measures such as immunization and safety measures.

National Security Decision 41 (14 February 1970)

The U.S. renounces offensive preparations for the use of toxins as a method of warfare. The U.S. will confine its military programs for toxins, whether produced by bacteriological or any other biological method or by chemical synthesis, to research for defensive purposes only, such as to improve techniques of immunization and medical therapy.

Biological Weapons Convention

Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. Signed in Washington, London and Moscow, 10 April 1972.

Article I

Each State Party to this Convention undertakes never in any circumstance to develop, produce, stockpile, or otherwise acquire or retain:

(1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;

(2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Article X

(1) The States Parties to the Convention undertake to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. Parties to the Convention in a position to do so shall also cooperate in contributing individually or together with other States of international organizations to the further development and application of scientific discoveries in the field of bacteriology (biology) for prevention of disease, or for other peaceful purposes.

(2) This Convention shall be implemented in a manner designed to avoid hampering the economic or technological development of States Parties to the Convention or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of bacteriological (biological) agents and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention.

An example of the broad-based research efforts being conducted by military microbiologists is the program to develop a malaria vaccine (Table 3). The work (see, e.g., Dame *et al.*, 1984, and Young *et al.*, 1985) of a group of scientists at WRAIR in collaboration with Navy microbiologists and researchers at NIH has resulted in cloning and expressing *Plasmodium falciparum* circumsporozoite proteins with the subsequent development of candidate human malaria vaccine.

A malaria vaccine alone may not be adequate in lessening the impact of this global disease. Therefore, WRAIR is developing new drugs or finding new uses for FDA approved drugs. A serious problem facing effective malaria therapy, especially in Southeast Asia and East Africa, is the emergence of drug resistant strains of *P. falciparum*. Mefloquine, which was developed and fielded by military microbiologists, is now being widely used to treat multidrug-resistant malaria. In addition, Klayman (1985) reported on the development of a new class of antimalarial compounds known as sesquiterpene lactones (called ginghaosu or artemisinin) that appear to be especially useful for treatment of cerebral malaria.

The medical biological warfare defense program is directed toward the development of vaccines and drugs to protect against potential BW agents (Table 4). All research is conducted in accordance with the *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and Their Destruction*, commonly referred to as the Biological Weapons Convention. In 1969, the United States unilaterally renounced biological warfare, destroyed its stock of weapons and has pursued only a defensive program in accordance with the 1972 Biological Weapons Convention (see Box).

The conventional approach to medical biological defense was based on the development of drugs and vaccines against specific agents. Potential threat agents were selected principally on criteria related to their ease of production, stability, and infectivity as aerosols. Products which have been fielded from this program have included vaccines for anthrax, tularemia, Q fever, and toxoids against five types of botulism. The advent of recombinant DNA technology has made it clear that the conventional approach of targeting drugs and vaccines against a specific organism may no longer be adequate. Rather than a limited number of organisms and toxins as originally considered, it now appears that the potential agents are limited only by the imagination of the scientist. To address this threat, emphasis has been placed on a broader and more generic approach. Research is being conducted to develop vaccines and therapeutic drugs against classes of agents with common mechanisms of action. For example, research centers on protection against groups of toxins which include protein synthesis inhibitors (e.g., trichothecenes), ion-channel blockers (e.g., saxitoxin) and pre-synaptic toxins (e.g., botulinum toxins). Research is also being conducted to evaluate drugs that are effective against a broad variety of infectious organisms. Of particular interest are compounds, such as interferon, which nonspecifically enhance the human immune system and provide a short-term, broad-spectrum immunity against several unrelated agents. Antiviral compounds are also being evaluated as nonspecific prophylactic and therapeutic drugs. One of the most effective of these is ribavirin, which is currently undergoing a double-blind placebo controlled trial against hemorrhagic fevers caused by Hantavirus, a member of the Bunyaviridae. Vaccines for antiviral diseases are also being developed with the objectives of being safe, live and polyvalent. An example is the use of vaccinia virus as a carrier for a number of RNA virus immunogens.

Rapid identification and diagnosis of infections in the field is another important component of the biological defense program. Systems currently under development will be

Table 3. Cases of Malaria, U.S. Army, 1965-1970

Year	Number of Cases
1965	1,972
1966	6,662
1967	9,124
1968	8 ,616
1969	7,322
1970	6,718
	TOTAL: 40,414

Table 4. Vaccines Developed Against Biological Warfare

Current Vaccine	Type
Venezuelan Equine Encephalitis	Live
Western Equine Encephalitis	Killed
Eastern Equine Encephalitis	Killed
Q Fever	Killed
Tularemia	Live
Anthrax	Purified Protein
Botulism	Toxoid (five types)

Rapid identification and diagnosis of infections in the field is another important component of the biological defense program. System currently under development will be able to detect a number of different agents including agents of naturally-occurring infectious diseases in infected soldiers. This information will support a presumptive prediction of the percentage of troops likely to become ill, the duration of the illness, the potential for epidemic spread, and the possible levels of medical support required.

The last program in which a significant number of microbiologists work is the Retrovirus Research Program (Table 5). This program, also know as the Medical Protection Against AIDS, is designated to explore technologies for the prevention and treatment of human immunodeficiency virus infections. As a major employer of young adults and a major blood collecting organization, the military recognizes that it should actively participate in the national effort to control AIDS. Research is directed to maximize the use of the unique characteristics of military populations: the broad cross-sectional

Table 5. DoD Retrovirus Research Program

Improved Methods of AIDS Detection (DX)
Natural History of AIDS in Military Population (NH)
Epidemiology of AIDS in Military Populations (EPI)
Vaccine Development (V)
Chemotherapy (RX)

nature of the community, their potential to be deployed to almost any area of the world, and the predominately heterosexual representation. Areas of research of military relevance include risk factor assessment and natural history of the disease; improved diagnosis; chemotherapy and drug evaluation; and human immune response mechanisms in the disease. Coordination with NIH and CDC, which have large standing research efforts on HIV, and the Veterans Administration, which is caring for many AIDS patients, has been an important part of this program.

In support of the programs previously mentioned (Figure 1), many universities throughout the world are awarded research grants or contracts to assist in the development of medical protective measures. These are a vital extension to any program that seeks to interrupt disease processes. There is also a very active resident research associate program administered by the National Research Council that provides post-doctoral positions. This includes participants from such countries as France, Sweden, India, the Philippines, and the People's Republic of China.

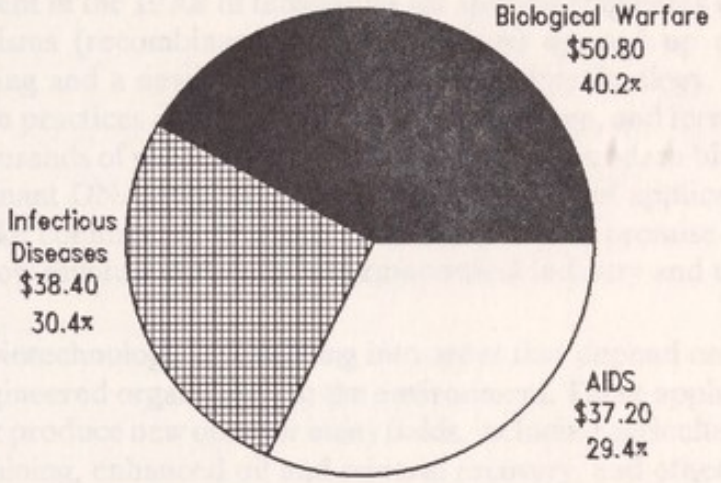

Figure 1. Military Disease Hazards Research Program Thrusts, FY 1986 ($M)

All of the above programs contribute to the improvement of world health and are guided by the following philosophy of the Disease Hazards Research Program. All research is conducted in an open, unclassified environment. Research is conducted in compliance with all appropriate regulations and guidelines (e.g., NIH, RAC, FDA, and EPA). Publication in refereed, scientific journals is encouraged as an important part of peer review. Finally, but of no less importance, is the participation of researchers in scientifically recognized societies and in other activities such as this symposium sponsored by the American Association for the Advancement of Science.

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New Developments in Biotechnology—Field-Testing Engineered Organisms: Genetic and Ecological Issues*

Office of Technology Assessment
U.S. Congress

Chapter 1: Summary, Policy Issues, and Options for Congressional Action

The development in the 1970s of techniques for splicing fragments of DNA from different organisms (recombinant DNA technology) opened up a new science of genetic engineering and a new industry, "molecular" biotechnology. The roots of this new industry lie in practices of animal husbandry, agriculture, and fermentation that extend back for thousands of years. To these ancient practices modern biotechnology adds not only recombinant DNA and cell culture, but also a host of applications using living organisms to make commercial products. These techniques promise to reshape many fields; they are now revolutionizing the pharmaceutical industry and medical diagnosis and treatment.

Commercial biotechnology is advancing into areas that depend on the introduction of genetically engineered organisms into the environment. These applications could improve old tools or produce new ones for many fields, including agriculture, forestry, toxic waste cleanup, mining, enhanced oil and mineral recovery, and others. In some cases, such as pest control or toxic waste management, successful development of biotechnological tools could reduce or phase out dependence on older, more hazardous chemical technologies. It is widely expected that the application of such biological approaches to many human activities will prove more benign to the environment than traditional technologies.

Planned introductions of genetically engineered organisms into the environment, often called *deliberate release*, are not, however, without potential risks. Virtually any organism deliberately introduced into a new environment has a small but real chance of surviving and multiplying. In some small subset of such cases, an undesirable consequence might follow. The complexity of even simple ecosystems makes the precise prediction of such events, and of their consequences, difficult.

This element of uncertainty has led some scientists, public officials, and private citizens to voice concern about the safety of planned introductions. Although there is some consensus in the scientific community that the likelihood of unique or serious problems from planned introductions is quite low, this opinion is not held unanimously. Some scientists cite the beneficial introduction of thousands of species of naturally oc-

*Excerpts taken from Chapter 1 of Office of Technology Assessment. 1988. *New Developments in Biotechnology–Field Testing Engineered Organisms: Genetic and Ecological Issues*, OTA-BA-350 (Washington, DC: U.S. Congress Office of Technology Assessment).

curring microbes, plants, and animals that have not adversely affected the environment. Other scientists point our that a small fraction of such introductions have become pests, and suggested that genetic modifications that permit engineered organisms to live in habitats new to them may, in some cases, present similar risks. There is also concern among some scientists that the genetic information newly added to existing species may sometimes produce undesirable changes in their ecological relationships with other species, or, in rare cases, be directly transmitted to other species.

The potential benefits of new biotechnologies have been widely reported. Thus, this report focuses primarily on questions raised by the critics. How do environmental risks from planned introductions of genetically engineered organisms compare to those encountered in the past in agriculture and commerce? How accurately can scientists predict the consequences of planned introductions? What genetic and ecological effects are possible or likely? What scientific and social issues need to be considered in developing risk assessment and management procedures? Does the introduction of genetically engineered organisms require new regulatory procedures to protect environmental and public health?...

Foremost among OTA's conclusions is that **there are reasons to continue to be cautious, but there is no cause for alarm**. Significant areas of uncertainty exist, particularly in the realms of microbial ecology and population dynamics. Widespread environmental or ecological problems do not now seem likely, however, though they could emerge in the future. If events develop other than as planned with a particular introduction, it seems more likely that the introduced organisms might become prematurely extinct, and consequently fail to perform as desired. While increased support for relevant research, both fundamental and applied, will reduce uncertainties, **some questions can be answered only with practical experience.**

Even though the range and complexity of applications of new biotechnologies means that the type of general models used for evaluating the risks from chemicals cannot be transferred easily, **adequate review of planned introductions is now possible**. A review process that involves critical study of planned introductions by experts with relevant knowledge and experience offers confidence of being able to anticipate and prevent most potential problems. As the number of such completed reviews increases one may expect some generalizable conclusions about the safety of different types of introductions. This should enable a consequent streamlining of the review process. And although almost any category proposed for exemption from review can be shown wanting through a hypothetical scenario, it is reasonable to expect that, with experience, broader categories will emerge for which less rigorous levels of review could be defended. Categories that could be examined now, at least for abbreviated review, include:

- organisms that could be produced with previously existing methods (e.g., mutagenesis and selection) which, if they were, would not be regulated under existing law;
- an organism substantially identical to one that has already been reviewed and approved for field testing;
- organisms not containing any genetic material from a potential pathogen; or
- organisms whose DNA contains nothing new but marker sequences in non-coding regions.

Regulatory agencies can and should move promptly to establish at least provisional categories for different levels of review. They should act subsequently to modify and streamline these as experience indicates. This will sometimes be a contentious exercise,

but the stakes, in terms of economic potential and environmental protection, are sufficient that there can be no substitute for common sense leavened by caution and appropriate flexibility. To guarantee essential public confidence, this also means that such decisions must be accountable, attributable to specific regulatory bodies, and sustainable by defensible and public reasoning.

With adequate review **none of the small-scale field tests proposed or probable within the next several years are likely to result in an environmental problem that would be widespread or difficult to control.** Indeed, greenhouse or microcosm studies are such inadequate predictors of field performance that in many cases **realistic small-scale field tests are likely to be the only way potential risks from commercial scale uses of genetically engineered organisms can be evaluated.** Assuming such small-scale field tests to identify areas of significant concern, there would be no scientific reason not to seek further experience with field tests or applications on a larger scale.

It is important to note that modifying organisms for specific human ends is not new; selective breeders of plants and animals have been transferring genes for millennia, often creating forms through centuries of selection that differ from their original stocks more than the forms produced by recombinant DNA methods. One of the distinguishing characteristics of the new technologies is that they allow scientists to do many of the same things as before with previously undreamed of precision and speed. In evaluating the potential risks associated with these new technologies, the appropriate question is not "How can we reduce the potential risks to zero?" but "**What are the relative risks of the new technologies compared with the risks of the technologies with which they will compete?**" Furthermore, **What are the risks posed by over regulating or failing to develop fully the new technologies? How do we weigh costs and benefits? How much review is enough?** In most cases the new potential risks will be qualitatively similar to the old risks. Sometimes they will be quantitatively less. The potential benefits to be derived are often substantial.

Anticipated Applications

Pending and potential environmental applications of genetically engineered organisms span an enormous range—enormous in terms of engineered organisms, the diverse environments into which they will be introduced, and the functions they are intended to perform (see Table 1-1).

Many pending or imminent introductions involve minor genetic alterations to modify an existing function in an existing organism. Most involve the activity of the product (protein) of a single structural gene. More than a dozen small- scale field tests have already taken place. Applications for others are pending or anticipated in the near future....

The Role of Public Perception and the Regulatory Regime

In many ways, the wide range of organisms and potential uses complicates the regulatory picture for the new industry of modern biotechnology because the **critical issues differ from application to application.** Policymakers need to rely on sound scientific review and weigh carefully any potential risks against anticipated benefits of each new planned introduction. **A flexible review process, founded in critical scientific evaluation and adaptable to the requirements of particular cases, can serve industry and the public interest well without being unduly burdensome.**

Table 1-1. Some Representative Pending and Potential Environmental Applications of Genetically Engineered Organisms

MICRO-ORGANISMS

Bacteria as pesticides. Ice-minus bacteria to reduce frost damage to agricultural crops.

Bacteria carrying Bacillus thuringiensis toxin to reduce loss of corn crops to black cutworm.

Mycorrhizal fungi to increase plant growth rates by improving efficiency of root uptake of nutrients.

Plant symbionts. Nitrogen-fixing bacteria to increase nitrogen available to plants, and decrease need for fertilizers.

Toxic waste disposal. Bacteria engineered to enhance their existing abilities to degrade compounds found in sludge in waste treatment plants.

Bacteria engineered to enhance their abilities to degrade compounds in landfills, dumps, runoff deposits, and contaminated soils.

Heavy metal recovery. Engineered enhancements possible to several species of bacteria now used to recover metals from low-grade ores (e.g., copper and cobalt).

Pollution control. Possible increased utility of bacteria in purifying water supplies of phosphorus, ammonia, and other compounds.

Viruses as pesticides. Insect viruses with narrowed host specifity or increased virulence against specific agricultural insect pests, including cabbage looper, pine beauty moth, cutworms, and other pests.

Myxoma virus modified so as to restore its virulence against rabbits (which became resistant during early biocontrol efforts in Australia).

Viruses as vaccines. Vaccines against human diseases including:

- hepatitis A and B
- polio
- herpes simplex (oral and genital)
- malaria
- acquired immunodeficiency syndrome
- rabies
- respiratory syncitial virus

Vaccines against animal diseases including:

- swine pseudorabies
- swine rotavirus
- vesicular stomatitis (cattle)
- foot and mouth disease (cattle)
- bovine rotavirus
- rabies (cattle, other mammals)
- sheep foot rot
- infectious bronchitis virus (chickens)
- avian erythroblastosis
- sindbis virus (sheep, cattle, chickens)

Multivalent vaccines. Vaccines possible for antigenically complex diseases such as:

- malaria
- sleeping sickness
- schistosomiasis

PLANTS

Herbicide resistance or tolerance to:

- Glyphosate
- Altrazine
- Sulfonylurea (chlorosulfuron and sulfometuron)
- Imidazolinone
- Bromoxynil
- Phosphinotricin

Disease resistance to:

- Crown gall disease (tobacco)
- Tobacco mosaic virus (and related viruses)
- Potato leaf roll virus

Pest resistance

BT-toxin-protected crops, including tobacco (principally as research tool) and tomato.

Seeds with enhanced anti-feedant content to reduce losses to insects while in storage.

Enhanced tolerance to environmental factors, including:

- Salt
- Drought
- Temperature
- Heavy metals

Nitrogen-fixation enhancements

Nonlegumes enhanced to fix nitrogen, independent of association with symbiotic bacteria.

Engineered marine algae

Algae enhanced to increase production of such compounds as B-carotene and agar, or to enhance ability to sequester heavy metals (e.g., gold and cobalt) from seawater.

Forestry

Trees engineered to be resistant to disease or herbicides, to grow faster, or to be more tolerant to environmental stresses.

ANIMALS

Livestock and Poultry

Livestock species engineered to enhance weight gain or growth rates, reproductive performance, disease resistance, or coat characteristics.

Livestock animals engineered to function as producers for pharmaceutical drugs, expeically of mammalian compounds that require post-synthesis modification in the cell.

Fish

Triploid salmon produced by heat shock for use as game fish in lades and streams.

Fish with enhanced growth rates, cold tolearances, or disease resistance for use in aquaculture.

Triploid grass carp for use as aquatic weed control agents.

The Effects of Public Perception

Public perception of the benefits and risks of biotechnology is as likely to influence future industry developments as is formal risk assessment by scientific groups and public officials. When proposing to field test genetically engineered organisms, scientists – whether in academic institutions or industry – must be prepared to work with local citizens and officials. Recent experience in several communities and an OTA-commissioned survey have shown that public opinion is ambivalent and can be vocal with respect to planned introductions of genetically engineered organisms. In several cases public opinion thwarted or delayed proposed field tests. In other communities opposition has been minimal, and in some cases vocal elements have been supportive.

The Existing Regulatory Framework

Shortly after recombinant DNA technology appeared and began to be more widely used during the 1970s, concerns were raised about its safety. In an unprecedented move, scientists developing the new techniques met in 1975 at the Asilomar Conference Center (Pacific Grove, CA), and agreed to control stringently their own research until the safety of the new technology could be assured. In 1976, the National Institutes of Health (NIH) issued the first formal guidelines for recombinant DNA research. As research continued, and as scientists learned more about the safety of genetically engineered organisms, initial fears proved excessive, the guidelines were repeatedly revised, and the controls on recombinant DNA research in the laboratory were relaxed.

Some of the safety concerns that have surfaced over the planned introduction of genetically engineered organisms are about issues quite different from those associated with research confined to a laboratory. Numerous ecological issues not relevant to laboratory work become important when applications move beyond the laboratory and into the environment. Assuming regulation is appropriate (an assumption challenged by some), who should regulate planned introduction experiments? How should regulatory agencies assess potential risks?...

The White House Office of Science and Technology Policy published the Coordinated Framework for the Regulation of Biotechnology in June 1986. This document identifies the agencies responsible for approving commercial biotechnology products and their jurisdictions for regulating field tests and planned introductions. It describes the regulatory policies of the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA), as well as the research policies of the National Institutes of Health (NIH), the National Science Foundation (NSF), EPA, and USDA. The purpose of the Framework is to enable the agencies to "operate in an integrated and coordinated fashion [to] cover the full range of plants, animals, and micro-organisms derived by the new genetic engineering techniques."

At present, FDA relies on its existing policies for regulating biotechnology products. EPA regulates biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). USDA relies on the Plant Pest Act and related statutes, while the Occupational Safety and Health Administration has regulatory authority over certain aspects of biotechnology that relate to workplace safety....

Genetic Considerations

The planned introduction of genetically engineered organisms that can survive and multiply raises a variety of genetical questions, many of which are relevant only if there

is a reasonable probability that the introduced organisms could have a deleterious impact on the environment or public health. The likelihood of such a consequence depends on the nature of the organism and on the new genetic information it carries. It also depends on whether the new genetic material in the altered organism remains where it was inserted, performing as designed, or is transferred to a new location in a nontarget organism, possibly performing in an unanticipated manner. It may therefore be important to consider, where such occurrence is plausible, the probability that novel genetic material will spread beyond the engineered organisms at the release site. The migration of genetic material from one organism to another by means other than germ cells is called horizontal transfer. In bacteria, horizontal transfer is the transmission of genetic information from one contemporaneous bacterial cell to another by whatever means.

What are the potential outcomes of such transfer? Are they beneficial, harmful, or of no consequence? How can the movement of genetic material be observed? What techniques or constraints can limit the frequency or mitigate any potentially adverse consequences of gene transfer?...

Predicting Potential Effects

...What are the conditions that encourage transfer or maintenance of the inserted genes, and how likely is it that genes could be transferred beyond the target site? If transferred, will the new genetic material be expressed? If transferred and expressed, will there be any environmentally significant consequences, positive or negative?...

Some observers maintain that if it is known that the gene in question will not move about, the potential consequences of gene transfer should not be a concern. Others argue that if the modified organism or gene will cause no problems if it does spread, then estimating the probability of transfer is unnecessary. Both issues must be addressed for a balanced evaluation of the potential consequences of a proposed introduction experiment. A very low probability of transfer multiplied by a moderate probability of hazard if transfer occurs produces a different situation than if both probabilities are very low. Of course, a significant probability of benefit could also offset all or part of any potential risk.

Other observers argue that it should be assumed that any introduced genetic material will eventually be transmitted to nontarget species, and that any consequences should be anticipated. Predicting the consequences and evaluating the risks of deliberate release requires information about intrinsic and extrinsic factors influencing the magnitude, frequency, and stability of gene transfer....

Monitoring Gene Transfer

Convenient, economical, and effective methods of tracking engineered organisms or the engineered gene(s) they contain are being developed. These can be divided broadly into selective and biochemical methods.

Selective tracking methods work by marking the host chromosome with antibiotic resistance genes or nutritional markers that confer a competitive advantage under specific conditions. When exposed to selection pressure exerted by the antibiotic, for example, organisms carrying the resistance gene survive and can be easily detected.

Such markers must be carefully screened, however, because those that confer an unintended competitive advantage – or that mutate to confer resistance to a whole family of antibiotics – could lead to problems. On the other hand, resistance genes are already present in many naturally occurring soil micro-organisms (a valuable source of new an-

tibiotics), and antibiotic resistance markers have long been used in studies of root ecology with no apparent ill effects.

When using nutritional markers the host chromosome can be marked with a metabolic gene (e.g., one coding for the production of an enzyme) not normally found in that organism....

As with antibiotic resistance gene markers, however, this may not always reveal if or how widely the engineered gene or construct may have traveled to other organisms. The movement of genes does not always correspond completely to the movements of the original host organism. To track the engineered gene itself, a selectable marker gene must remain where it is inserted, close to the gene to be tracked; the two would most likely be transferred together (depending on how closely they were linked), making it possible to locate the engineered gene by selecting for and isolating any cells with the marker gene.

Biochemical methods often rely on gene probes made with recombinant DNA techniques. A gene probe is a segment of DNA whose nucleic acid sequence is complementary to the gene of interest, or to a portion of it. The probe is labeled with radioactivity or marked with a dye that can be easily detected in the laboratory. A gene probe will track a gene even if it is separated from a tightly linked selection marker or in an organism that cannot itself be cultured. But to quantify gene transfer would require general tests of all microbes or DNA in the release environment; processing large numbers of samples would be difficult and expensive.

Inhibiting Gene Transfer

As with detection and tracking, techniques to prevent or reduce horizontal gene transfer are not yet well developed. Researchers can either choose or modify the host and/or the vector so that introduced organisms have a low probability of persisting in the environment, of transferring genetic material, or both. Specific choices and modifications will depend on the characteristics of the organisms involved and the purpose for which they are engineered.

Whereas gene transfer may be a legitimate concern in planned introduction of some bacteria, it is unlikely to be a general concern with plant DNA vectors even when the most active plant vectors are used. Nor is gene transfer a concern in organisms engineered by gene deletion, though other traits may then by important.

Reducing or eliminating the use of mobile plasmids and transposons could also help minimize horizontal transfer....

In another approach, and EPA research group is working to construct a "suicide" bacterium designed to persist in the environment only as long as it is needed. The bacterium contains a plasmid carrying a gene that functions only in the presence of the toxic substance the bacterium is designed to clean up; when the toxic substance is no longer available, the plasmid self-destructs.

Ecological Considerations

The major ecological concern over planned introductions of genetically engineered organisms into the environment stems from the potential for unforeseen or long-term consequences. **Although there are enough uncertainties that introductions should be approached with caution, a large body of reassuring data, derived chiefly from agriculture, supports the conclusion that with the appropriate regulatory oversight, the field tests and introductions planned or probable in the near future are not likely to result in serious ecological problems....**

The worst possible ecological impact a planned introduction could have would be to disrupt a fundamental ecosystem process, e.g., the cycling of a mineral or nutrient, or the flow of energy in an ecosystem; such disruptions are not, however, among the credible consequences of any introduction that seems likely within the next several years. The high degree of functional redundancy among species (particularly microbes) involved with such processes (e.g., nutrient cycles or energy flow) and the resilience and buffering in natural ecosystems are persuasive arguments against the likelihood of such consequences.

Although predicting ecological consequences of planned introductions is complex, researchers and regulators are addressing the questions raised by such introductions. Five criteria have been laid out for evaluating the likelihood of environmental impact:

1. **Potential for Negative Effects:** If it is known that a recombinant organism will have no negative effects, there is no cause for concern. But predicting ecological effects, their probability, and assessing whether they are negative or positive is not always straightforward.
2. **Survival:** If a genetically engineered organism does not survive, it is unlikely to have any ecological impact. It is also unlikely to fulfill the purpose for which it was engineered (unless brief survival was all that was required).
3. **Reproduction:** Some applications require not only survival of the recombinant organism but its reproduction and maintenance. Increasing numbers could, in some settings, increase the possibility of unforeseen consequences.
4. **Transfer of Genetic Information:** Even if the engineered organism itself dies out, its environmental effects could continue if the crucial genetic material were favored by selection and transferred to and functioned in a native species,...
5. **Transportation or Dissemination of the Engineered Organism:** A recombinant organism that moves into nontarget environments in sufficient numbers could interact in unforeseen ways with other populations or members of other communities....

Potential Impact on Populations or Communities

Local populations or communities can be affected by the introduction of organisms (engineered or not) that are:

- slightly modified forms of resident types,
- forms existing naturally in the target environment but requiring continual supplements to function,
- forms existing naturally elsewhere that have not previously reached the target environment, or
- genuine novelties....

Plant Communities

At present, most plant genetic engineering focuses on introducing into crop plants genes that confer resistance to herbicides or pests, and these alterations are technically among the easiest to accomplish. The market for herbicides and pesticides is profitable and flexible.

A prominent concern is that herbicide-resistance genes may spread into weedy relatives of crop plants, most likely by sexual reproduction. If the genes spread to weeds against which the herbicides are targeted, the herbicides become less effective.

One considerable genetic engineering effort against a specific pest involves the insertion into plants of genes coding for toxins from *Bacillus thuringiensis* (BT). These bacterial compounds are highly effective pesticides against the young larvae of butterflies, moths, and some beetles. Farmers have applied BT to their fields in large quantities for decades. Rohm & Haas (Philadelphia, PA) and Monsanto (St. Louis, MO) have already carried out successful field tests in which engineered tobacco and tomato plants to which BT toxins were added gained protection from predation by caterpillars.

The simple presence of large quantities of BT toxin in the environment is not worrisome because it is not toxic to humans or animals, and it decomposes in a relatively short time. Produced inside crop plant tissues, however, BT toxin is protected from environmental degradation, thus extending its persistence as it provides season-long pest control. However, this might introduce a problem of a different kind: such an approach also lengthens the time that less susceptible individuals (e.g., late larvae and adults) of the target species may be exposed to the toxin, and thus subjected to selective forces that can be expected to lead to evolution of resistance in those populations....

[An] immediately practical solution is based on the observation that pathogens and pests adapt more quickly to the defenses of prey species in a genetically homogeneous community, such as a cultivated field, than in a genetically diverse one. Increasing the variation in the genes controlling defenses against pests should slow the pests' adaptive response. Genetically pest-resistant crop plants could be mixed, for example, with unprotected plants. A smaller proportion of protected plants will exert lower selection pressures on the insect populations, slowing their evolution of resistance. Yet they would still offer enough protection to preempt the growth of swarms of herbivorous insects that cause the most crop damage. This approach is based on a strong theoretical and experimental foundation, and is well within the capability of existing technologies.

Insect Communities

Because they inflict so much damage on agricultural products, insect communities have become the target of recombinant plants, microorganisms, and insect predators engineered to check them. Two representative examples are the bacterium *Pseudomonas fluorescens*, which has been altered to enable corn to resist the black cutworm, and a class of viruses that parasitizes certain pests.

The black cutworm feeds on the roots of corn plants, causing significant corn crop losses. It is vulnerable to BT toxin. Monsanto scientists have used a special vehicle called a transposable element to insert the gene for BT toxin into *Pseudomonas fluorescens*, which lives among corn roots. The transposable element has been altered to make it unlikely that the inserted gene can move beyond its insertion point or leave its *Pseudomonas* host. Preliminary tests suggest that the bacteria do not move beyond the roots they colonize initially, nor are they likely to persist in a field from season to season.

Baculoviruses, rod-shaped viruses that are specific pathogens to one or a few closely related insect species, are being developed to target insect pests, including the cabbage looper and pine sawfly in the United Kingdom. Initial tests involved inserting a marker DNA sequence into the virus to enable scientists to track it. Researchers hope this work will produce a better understanding – and therefore better control – of the dispersal of such altered viruses, as well as of the genetics of host specificity.

Microbial Communities

Microbes can be and are being altered for many uses. Two of the most useful potential applications involve altering root-inhabiting micro-organisms to increase the amount of nitrogen they fix...and inoculating plants with altered bacteria to enable them to resist frost damage.

The introduction of ice-minus bacteria has been a source of some controversy among the lay public. The cell membrane of some bacteria contains a protein encoded by a single gene that acts as an efficient nucleus for the formation of ice crystals on the surfaces of plant leaves or blossoms where the bacteria live. Without such a nucleus, ice crystals do not form until about 9°F below freezing. Crop losses to frost damage in the United States average about $1.6 billion per year. Scientists reasoned that removing the ice-nucleating gene from the bacteria and using them to colonize crop plants could confer a measure of frost resistance on the host plants and eliminate at least a portion of the annual crop loss.

Small-scale field tests of this ice-minus system present little risk: Ice-minus mutants are present in natural bacterial populations....Nevertheless, some observers of these field tests have been concerned about a possible worst-case scenario, albeit one that could only apply to large-scale uses of ice-minus bacteria....

If ice-minus bacteria were widely applied in agriculture, some claim, the atmospheric reservoir of ice nuclei might grow smaller, changing local or perhaps even global weather patterns. Some possible support for this argument comes from Africa's Sahel desert, where overgrazing has reduced already sparse vegetation. In this scenario, the reduction in ice nuclei due to overgrazing may have contributed, in turn, to decreasing precipitation, further reducing vegetation.

Several different studies suggest, however, that even under a long chain of worst-case assumptions (many of which contradict known facts) the alteration of climatic patterns through large-scale agricultural applications of ice minus bacteria is not likely. Many of these assumptions, however, could benefit from being tested by further research.

Potential Impact on Ecosystem Processes

Ecosystems are enormously complex and, as a rule, not well understood. Associations of plants, animals, and micro-organisms interact with one another and with their physical environment so as to regulate the flow of energy through the system and the cycling of nutrients within it. The major force driving these processes is capture of the sun's energy by photosynthetic plants and its storage in biologically accessible carbon. Carbon and all other substances vital to living things circulate within ecosystems in biogeochemical cycles. Any major perturbation of these cycles could not only affect living organisms but might disrupt the functioning of ecosystem processes. Much evidence, however, suggests that major perturbation is unlikely.

Given the complexity of ecosystem associations, interactions, and processes, it is not surprising that introducing a genetically engineered organism into the environment has raised concerns. Ecosystems, however, by the very complexity that makes them difficult to understand, are buffered and often resilient in the face of perturbations. **While fundamental disruptions of ecosystems should be guarded against, historical experience with both accidental and intentional introductions suggests that such risks are not likely consequences of any planned introductions of genetically engineered organisms being considered now or likely in the near future....**

Risk Assessment

Most researchers and policymakers agree that although there is no general methodology for predicting and evaluating the risks of planned introductions, a flexible, mechanism for review of those that might pose some risk has, for the time being (the next several years), much to recommend it. It offers a high likelihood of anticipating potentially significant problems that might arise and of revealing the kinds of planned introductions that will merit the closest scrutiny as well as those that might require little or none....

An important element in approaching the current regulatory framework for regulating planned introductions is to distinguish risk assessment from risk management. Risk assessment is the use of scientific data to estimate or predict the effects of exposure to hazardous materials or situations; the process may be qualitative or quantitative. Risk management, on the other hand, is the process of weighing policy alternatives to select the most appropriate regulatory strategy or action. Risk management depends on the scientific findings of risk assessment, but also takes into account technical, social, economic, and political concerns. It is influenced by public opinion and requires value judgments: How acceptable are the potential risks of genetically engineered organisms in the environment relative to their benefits and the costs of controlling them?...

Micro-Organisms v. Macro-Organisms

Ecological, genetic, and evolutionary impacts resulting from size differences among organisms must be considered in assessing the risks of their release. Particularly from ecological and evolutionary standpoints, micro-organisms present greater uncertainties than do macro-organisms, though it is not clear this means they present greater risks. Although most macro-organisms are large, and thus relatively easy to track, many insects, weeds, and vertebrates that were introduced have been impossible to exterminate. Most investigators agree that microbes are more difficult to track and control than macro-organisms, though not all agree this means microbes pose greater problems. On the other hand, the life history and population models now available to researchers often fit micro-organisms better than macro-organisms, making them in some ways easier to study.

Although their large size means macro-organisms can move more biomass or cycle more nutrients through an ecosystem per individual than micro-organisms can, they are not as numerous. The rapid reproductive rates and easy dispersal of small organisms could allow them to proliferate and spread faster through the environment than large ones. And although micro-organisms play key roles in fundamental ecosystem processes, functional redundancy among members of microbial communities seems to provide a greater degree of resilience to environmental perturbations than macro-organisms enjoy.

Evolutionary lability is an important consideration in biological risk assessment: Any assessment of risks, no matter how thorough, would be inadequate should the engineered organisms evolve traits they did not have when released. The potential for a population to evolve depends in part on the numbers of individuals in that population, but most importantly on the selective forces involved. **Therefore all reviews of planned introductions, particularly those involving microbes, should carefully scrutinize the selective forces that will be involved and the likely consequences of selection on the introduced organisms.**

Implications for Research

Some of the controversies surrounding the initial attempts to release genetically engineered organisms into the environment have pointed out gaps in knowledge about ecological systems. Current and proposed small-scale field tests will undoubtedly begin to fill some of these gaps and contribute to the development of better risk assessment protocols, but more than this is needed....

Taxpayers are investing much to develop science and technology, but relatively little to develop means for ensuring the safe and wise application of such knowledge. Funding for science and technology, and the resulting research, is very uneven across fields...[T]he basic knowledge necessary to assess the performance of a technology often remains undeveloped, even as the technology is being refined for use. Research on the ways in which biotechnology may influence natural and managed ecosystems, how to assess its risks and benefits, and how to manage it as a technology, should perhaps be viewed as part of the cost of developing the technology. Research areas that need to be stressed include:

- test systems, such as aquatic and terrestrial laboratory microcosms, where ecological interactions can be analyzed before actual release – although such tests are not sufficient substitutes for field tests, they provide essential information needed in considering the potential consequences of planned introductions;
- the classification and relationships of organisms in natural populations (taxonomy and systematics), especially the genetic relationships of colonizing species or those organisms related to candidates for engineering and planned introductions;
- natural history of organisms planned for genetic alteration and release;
- interactions within natural and managed microbial communities (microbial ecology and population dynamics); and
- more efficient and convenient monitoring and tracking techniques for use in microbial studies;...

Policy Issues and Options for Congressional Action

Three policy issues related to the planned introduction of genetically engineered organisms into the environment were identified during the course of this study. The first involves the development of scientifically founded criteria for the review of planned introductions of engineered organisms. The second concerns actions that Congress might take to shape or direct regulatory policy toward the review and regulation of planned introductions. The third relates to actions Congress might take to affect the development of information and trained personnel that will be needed in the future to ensure that planned introductions continue to be carried out safely.

Following each policy issue several options for congressional action are listed, ranging from taking no specific steps to taking major action...The order in which options are presented does not imply their priority. Furthermore, the options are not, for the most part, mutually exclusive...A careful combination of options might produce the most desirable effects.

ISSUE: What criteria should be used to review applications for permission to field test planned introductions of genetically engineered organisms?

Scientists do not now agree that there is a clear scientific need for a review process by different mechanisms or according to different criteria for engineered organisms intended for environmental introduction than are now being applied to nonengineered organisms.

Option 1: An organism engineered for planned introduction into the environment should not require pre-release review simply because it was produced via recombinant DNA techniques.

With this approach, planned introductions of engineered organisms would not be reviewed according to criteria or mechanisms any different than would be required for the same introduction if it did not involve an engineered organism. A review process organized in accord with this option would have the advantage of focusing exclusively on the product and its characteristics, rather than the process used to produce it. This approach could be most easily adapted to existing regulatory authorities and the mechanisms through which they are administered. One disadvantage is that some potential problems associated with engineered organisms are different than most of the problems existing regulatory authorities handle, e.g., problems stemming from the ability of living organisms to grow, reproduce, or transmit genetic material to nontarget species. It is also possible that some engineered organisms will raise significant, new questions that regulators would overlook, absent special review. However, such problems are not entirely new; some are familiar, already regulated aspects of existing practices, especially in agriculture. Nevertheless, even if there is no clear need for a new regulatory approach, planned introductions of genetically engineered organisms could benefit from some review at least for the foreseeable future, even if only to provide public reassurance that field tests of engineered organisms are not unduly hazardous.

Option 2: All proposals to introduce genetically engineered organisms into the environment should receive the maximum possible pre-release scrutiny.

The advantage of this approach is that it is most likely to ensure that potential hazards associated with field tests of any planned introduction will be discovered and eliminated. The disadvantage is that very few planned introductions, at least for the foreseeable future, seem likely to present significant hazards. Substantial resources could be committed to unnecessary review; the personnel and resources of regulatory agencies would be strained or swamped, and significant impediments would be placed in the path of researchers attempting to develop products.

Option 3: Planned introductions should be reviewed on an adaptable, case-by-case basis, according to scientific criteria that are agreed upon and consistent, and tailored to the specific questions posed by particular applications.

Any specific set of criteria is likely to be somewhat contentious. This will be especially true of any criteria intended to apply to separate proposals that would be reviewed by different agencies. However, the broad outlines of a regulatory approach that should be generalizable are clear: **it should be possible to sort all applications for permission to field test engineered organisms into broad categories for which low, medium, or high levels of prior scrutiny will be appropriate**. Assigning an incoming application to a level of review must, of course, be done on a case-by-case basis. This does not mean that all applications for permission to field test will require the same level of scrutiny: they should not. Nor does it mean that the review of each application should begin *de novo*, without

regard to past experience with engineered organisms or relevant knowledge gleaned from the study of nonengineered organisms. Such background information is essential to expeditious review.

As experience accumulates, assuming no untoward developments, since the majority of planned introductions are not expected to generate problems, the presumption of low level review might be extended to a broader range of proposed field tests. Conservative standards that could be useful in sorting proposals into the appropriate review category might include criteria like the following:

- Low Review:
  Product is functionally identical to one already reviewed and approved for field testing.
  Product is functionally identical to others that can be produced with nonrecombinant DNA techniques.
  Product will entail lower levels of risk to the environment or to public health than existing products with which it will compete.
  Product differs from naturally occurring organisms only by the addition of noncoding marker DNA sequences to noncoding regions of the DNA of the recipient.
- Medium Review:
  Product is different in some ways, but generally similar to previously existing products in general use.
  Product entails substantial probability of new genetic material being transmitted to nontarget organisms in application environment or beyond.
  Product entails significant probability of altering community into which introduced.
- High Review:
  Product involves the transfer into a new host organism of disease genes derived from a pathogenic donor.
  Product is a genuine novelty with which there is little or no previous experience that can serve as a guide to risk assessment and management.
  Product entails substantial probability of disrupting community into which introduced.

ISSUE: What administrative mechanisms can regulatory agencies use to apply such criteria to the review of applications for permission to field test planned introductions of engineered organisms?

Option 1: Allow regulatory agencies independently to develop and apply criteria for reviewing applications for permission to field test planned introductions of engineered organisms.

This would permit regulatory agencies to develop criteria for sorting and evaluating planned introductions of engineered organism with exclusive attention to applications falling within their separate jurisdictions (e.g., engineered plants by USDA or engineered microbes by EPA). The advantage to this approach is that agencies need not consider issues that would be important only to applications under the jurisdiction of another agency. The drawback to this approach is that different agencies might regulate

according to disparate standards or criteria, leading to inconsistent levels of review, regulation, or enforcement.

Option 2: Direct regulatory agencies to develop in coordination with one another, but not by any particular process, specific criteria for classifying and reviewing applications for permission to field test planned introductions of engineered organisms.

This was the original intent of the Coordinated Framework established by the Administration on June 26, 1986 (51 *Fed. Reg.* 23301). In order for this option to function well, however, effective leadership is needed from a coordinating authority. Under the Coordinated Framework, it was intended that this role be fulfilled by the Biotechnology Science Coordinating Committee (BSCC). As it is presently constituted, the BSCC lacks the power to impose its decisions upon the regulatory agencies, or to eliminate disparities in approach by different agencies. Criteria for review that have emerged under this framework to date have not been entirely consistent among agencies. In addition, basic tasks, such as the adoption of commonly agreed upon definitions for "deliberate release," have not yet been accomplished.

Option 3: Provide an interagency group with the power to direct the coordinated development of criteria for classifying and reviewing applications for permission to field test planned introductions of genetically engineered organisms.

This would produce a system similar to that embodied in the Biotechnology Science Coordinating Committee and outlined in the Coordinated Framework, except that the coordinating body would be created by Congress and would have specific powers. Such a body, created by Congress, could be composed of the same or different members as the BSCC, organized within the Office of Science and Technology Policy, or created elsewhere. It would have the authority to direct the preparation of review standards to be used by regulatory agencies according to consistent criteria, and to standardize regulatory approaches as much as possible among different agencies. It could develop such standards independently or in conjunction with the relevant agencies.

ISSUE: Is research supporting the planned introduction of genetically engineered organisms adequate?

Option 1: Take no action.

A significant amount of research is now funded by the Federal Government in areas that contribute to the knowledge base required for sound review and regulation. Principal agencies now sponsoring or conducting such research are NSF, NIH, USDA, and EPA. Such research will likely continue in the absence of additional, targeted appropriations. An example of the type of research likely to be productive is the recent OSTP sponsored initiative, jointly funded by NSF, USDA, and DOE, to fund interdisciplinary, fundamental research in several targeted areas of plant science.

Option 2: Establish an interagency task force to coordinate interdisciplinary research.

Whether or not funding is increased, the different agencies funding relevant research (NSF, USDA, NIH, and DOE) could increase their coordination in the sponsoring of new research initiatives. The recent collaboration between NSF, DOE, and USDA in the establishment of an initiative for research in plant science might be an appropriate model.

Option 3: Increase research funding to selected target areas.

If funding is increased to selected areas, it could most profitably be directed to the divisions of funding agencies sponsoring most of the relevant research. These include, at NSF, the Directorate for Biological, Behavioral, and Social Sciences, and its components, the divisions of molecular biosciences, biotic systems and resources, information science and technology, and others; the National Institute of Environmental Health Sciences and the National Institute of General Medical Sciences at NIH; components of the Division of Science and Education at USDA; and at DOE, the Office of Health and Environmental Research in the Office of Energy Research.

Particular value is likely to be derived from funding earmarked for interdisciplinary studies, or collaborations between scientists in the various disciplines important to understanding and predicting the consequences of environmental perturbations. **Emphasis should be given to studies focusing on the single most important factor affecting the fate and consequences of planned introductions: natural selection**, or the selective interactions between competing organisms, and the selective pressures on organisms due to environmental factors. Other promising areas include basic research in molecular and developmental biology, studies of gene regulation, microbial ecology, community interactions and processes, and evolutionary and ecological relationships.

The disadvantage of such targeting is that it assumes the specific areas where the most important research should be done can be accurately predicted. The results of research are, by nature, unpredictable; this may be especially true of the interdisciplinary research important to planned introductions. Administrative flexibility and adaptability would therefore be important in any such programs, along with the avoidance of undue specificity in the targeting of funds.

Risk assessment and management are vital areas that will increase in importance with the numbers of planned introductions. They lack, however, a strong, vocal constituency to argue for increased funds. The primary agency now funding such studies is EPA, and much of the sponsored research is applied in nature. Both EPA and NSF could be encouraged to enhance their support for basic research relevant to biotechnology research assessment. In the absence of a strong, organized, vocal constituency to help advise on the most effective program, progress might be driven by allocating for risk assessment and management research a fixed proportion of the funding designated for research in other relevant areas.

Public education specific to biotechnology is another important area presently lacking a strong constituency to argue for improvements. [It] could be achieved through actions taken by the Science Education divisions of both NSF and USDA. Specific measures might include brochures and pamphlets, newsletters, public conferences and debates, yearbooks and annual reports, and extension service activities.

Option 4: Increase personnel education and training.

Because they already have similar programs, the primary agencies to administer any new training programs would logically be NSF, NIH, and USDA. For the near future, the most effective investment would be in programs to provide mid-career training for established investigators. Other valuable programs could include funds for graduate student and postdoctoral training.

There is an urgent need for scientists who are neither molecular biologists nor ecologists, but investigators comfortable with and competent in the techniques and background knowledge of both areas, able to use whichever tools are appropriate to the task. Interdisciplinary training is vitally important to the production of such investigators. Part

of the reason there is not more research now being done to develop methods of predictive ecology and risk assessment has to do with historical neglect of these areas by funding agencies, since recognition of their importance has been slow to emerge. But as funding availability has increased in the recent past there has been a relative shortage of investigators applying for or trained to carry out such research.

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