ISSUE DEFINITION

Technical discoveries of the past 10 years in the field of molecular genetics have greatly expanded the horizons of industrial microbiology. These new techniques provide the framework for the speciality commonly referred to as genetic engineering. This expertise enables the researcher to recombine DNA (the hereditary material of the cell) in a very precise manner. The same techniques can be used to manufacture products which have never been produced before by bacteria and to manufacture products at a higher rate and yield than previously possible. While the controversy concerning the ethical issues associated with this new biochemical tool seems to have abated somewhat, a new concern has arisen: the role of the university in the commercialization of genetically engineered products which are developed on campus. Congress has begun to address whether commercialization will have an adverse impact on university biomedical research and, if so, whether there are mechanisms available to protect the interests of the university.

BACKGROUND AND POLICY ANALYSIS

The issues associated with the commercialization of university research recently received public attention due to the announcement by Harvard University that it was considering the formation of a new biotechnology company. On Oct. 9, 1980, President Derek Bok released a "Discussion Memorandum on Technology Transfer at Harvard University" to the faculty for its consideration. The memorandum reviewed in general terms the formation of a new company, in conjunction with a Harvard professor and outside venture capital, that would make use of patents held by the University. Harvard would have been given a minority share (10%) in the company, and in return the company would have received the rights to use the University's patents. The many drawbacks to such a venture were also reviewed. The memorandum drew extensive criticism, not only from the Harvard faculty but also from the media and other universities. On Nov. 17, 1980, President Bok announced that Harvard had decided for a variety of reasons not to become a minority shareholder in the new biotechnology company.

The more general issue of the relationship between commercialization and university research, however, is not unprecedented. Industry and the academic community have long recognized that they have many mutual research interests. During the first decades of this century, many liberal arts colleges were expanded and rapidly transformed into research centers for the emerging electrical and chemical industries. The financial ties between the two gradually weakened, however, following World War II as government spending for research on defense, nuclear energy, and medicine increased. In the mid 1950s the Federal Government provided about 55% of the support for university research. Industrial firms supplied 8% of the funds while the remaining 37% came from foundations and State and local governments. By the late 1960s, the Government's share had expanded to more than 70% while industry's share fell to under 3%.

Lately, however, the trend appears to be changing: industry support is increasing relative to that of the Federal Government. Private companies are searching for technological innovations to help offset growing competition from abroad, falling productivity, and rising energy costs. The companies also realize that as an adjunct to their own in-house research efforts the
Universities are a relatively inexpensive source of new ideas. The duplication of facilities and staff available would be both wasteful and nonproductive. On the other hand, the universities are in need of new funding sources to offset shrinking enrollments, fiscal austerity, and the overall decline in government support of research.

The desire to lessen the regulations associated with the expenditure of federal dollars also influences the universities to increase their reliance on industrial funding. The amount of time spent by researchers in compliance with federal regulation has been increasing over the years. It has been estimated that in 1975 the faculty of Harvard University spent 80,000 hours filling out forms in compliance with federal regulation. The amount of time is certain to increase with the implementation of Circular A-21 (released Feb. 25, 1979) from the Office of Management and Budget, which requires that each individual scientific investigator inform the government how he spends 100% of his professional time, even if he is not entirely supported by federal grants. Yale University recently (Mar. 22, 1982) declined a $30,000 federal grant when it decided not to comply with the regulation in circular A-21. An article in Science (1980; 210: 34-37) has estimated that Circular A-21 would increase the number of forms filed with Washington from 3000 to 80,000 in the coming year. The less the dependence on federal support, the greater the freedom from federal regulation.

There are many ways in which the academic community may participate in the commercialization process. Perhaps the simplest and most well established is to obtain exclusive licenses of university patents. In general, however, molecular biologists have been less active than chemists and engineers in obtaining patents, perhaps because their work, until recently, has lent itself less often to commercial applications. In addition, medical discoveries tended to remain unpatented since the tradition of dedicating health-related research to the public was generally observed.

Another arrangement is the research partnership in which one university and one company work together on a single project. The Harvard University/Monsanto arrangement is an example of such a partnership. In 1974, after a year and a half of negotiations, Harvard and Monsanto signed an agreement that over a period of 12 years Monsanto will give the University $23 million in research support, laboratory space construction, and endowment money. In return, Harvard gave Monsanto the patent rights on TAF (tumor angiogenesis factor), a biological substance which may be involved in the growth of cancerous tumors. The agreement was touted as an original, imaginative, and precedent setting arrangement.

The research consortium, another collaborative effort, is becoming increasingly popular. It joins a single university with a group of companies that are interested in a common area of research. The NSF (National Science Foundation) introduced the idea several years ago and provided the initial funding for a number of programs. Among the leading industry-funded consortia are the MIT Polymer Processing Program and the Carnegie-Mellon Robotics Institute.

A less formal version of the research consortium is the industrial associates (or affiliates) programs. These are short term arrangements in which university scientists visit companies, listen to their problems, and explore approaches to solving them; these activities lay the groundwork for future cooperative efforts. Stanford University's biochemistry department, after rejecting a proposal similar to Harvard's, has decided upon an industrial affiliates program under which companies will give the University
$12,000 annually. In return the companies will be able to send representatives to a seminar on the department's work, to receive one visit per year from a faculty member for discussions on the company's research, and to send a representative to Stanford to discuss this research with the faculty. Stanford scientists feel that this arrangement allows them to avoid direct commercial involvement while still seeing that research results reach the public domain. The University of Wisconsin runs more than 100 separate projects of this sort ranging from forestry and fisheries to genetic engineering.

On a smaller scale than the industrial affiliates/associates programs are the individual arrangements between a single faculty member and a particular company. These can range from simple consulting contracts to partial ownership/founder relationships. Herbert Boyer's (University of California, S.F.) tie with Genentech is an example in the genetic engineering field of a partial ownership/founder relationship.

A few new companies have emerged which attempt to bridge the gap between the individual researcher or university and private venture capital. The much publicized DNA Science of E.F. Hutton is one such company. DNA Science recently (August 1981) underwent a transformation which would enable it to capitalize on a new tax law, P.L. 97-34, and allow the creation of a series of tax-advantaged partnerships. The partnerships will allow the firm's customers to invest in biotechnology and at the same time receive substantial tax benefits. P.L. 97-34, the Economic Recovery Tax Act of 1981, allows among other things a 25% tax credit for 65% of all of an investor's payments to universities for basic research. The new law also permits a larger deduction for charitable contributions of equipment used in scientific research. A similar idea has been put forth by University Genetics (or Ugen), a private company owned by University Patents. The parent company is an established business which patents technologies or inventions developed by university scientists and then licenses them to commercial concerns. Ugen emerged last October and has since raised over $30 million in capital. It provides a function which allows for private investment in university research on genetic engineering and related topics.

Public Law 96-517 (the Patent and Trademark Amendment Act of 1980) gave organizations such as Ugen a freer hand in this type of research funding arrangement. The law took effect July 1, 1981, and provides a single Government-wide policy on the allocation of patent rights resulting from federally supported research with preferential benefits for universities, small business firms, and non-profit organizations. P.L. 96-517 requires that (with certain exceptions) small businesses, universities, and non-profit institutions be given preferential title rights to inventions made under federally funded R&D. Currently active grants are not affected under P.L. 96-517, but new funding arrangements made after July 1, 1981, are covered. Its intent is to encourage cooperation between universities and industry by allowing the universities to offer future licenses in exchange for support even if Federal money is involved.

Even though commercialization of academic research is not an entirely new issue, there has been considerable discussion and controversy over the entrance of biomedical research into this arena. Recent articles written on the subject often mention that there are many differences between the commercialization of physics and chemistry and what is now happening in biomedical research. The following are some of the differences which have been cited, and perhaps account for this increased controversy.
(1) Commercialization of biological techniques seems to have occurred much faster than previous instances in chemistry and physics.

(2) The commercialization experience in biology is thought to involve a much broader spectrum of expertise in its participants than was the case previously in chemistry and physics. The new technology involves many individuals with interests in genetics, biochemistry, cell biology, microbiology, immunology, development, etc., while commercialization in the physical sciences frequently involves only a small number of specialists.

(3) The range of application seems to be much greater than in the commercialization of discoveries in the physical sciences. The areas of agriculture, medicine, waste disposal, specialty chemicals, energy, and oil recovery all have the potential for future innovation by recombinant DNA techniques and have caught the interest of researchers and the private capital of industry.

It may also be the case that since this is the first time biology has a major technology which is saleable, the biologists are merely experiencing the growing pains that physicists and chemists went through 50 years ago.

Whether or not biology is a case of commercialization distinct from chemistry and physics, there have been a number of objections raised to its commercialization. Foremost is the issue of secrecy, which is frequently widespread in highly competitive fields of even basic research. Often a scientist will not discuss the results of his work until he is sure that his methodology and assumptions are correct. The possibility that a research discovery may be patented is often cited as a source of secrecy. While patentability may contribute to secrecy over the short term, in the long run it eliminates the need for secrecy. After the filing date of a patent application, the information is at that point in the public domain and can then be used for discussion and noncommercial use by others.

In the scientific community of the university, secrecy can be the source of friction and conflict. For example, at Harvard two researchers in the same department are part owners in different genetic engineering companies: Walter Gilbert of Biogen, a Swiss-based company, and Mark Ptashne of the Genetics Institute. The Harvard proposal mentioned earlier may have complicated matters even further if it had been approved, for the faculty would have included those associated with "Harvard Company", those with other industrial affiliations, and faculty members without commercial ties. Questions may have been raised as to whether the university administration would have treated certain faculty members preferentially in terms of space allocation, hiring, and promotion. However, as pointed out in a recent issue of the New England Journal of Medicine (May 14, 1981, p. 1232), the problem of preferential treatment is not unique to situations involving commercialization. Faculty salaries for an entire research department are sometimes drawn from grants to individual faculty members. Thus, the influence on appointments in a department by individuals who are capable of bringing with them external funding may be considerable.

As faculty members become increasingly involved with outside companies (i.e., from consulting arrangements, to part ownership, to company officers), critics question whether they will be able to remain equally dedicated to
campus activities such as teaching undergraduate students and guiding the research efforts of graduate students. The development of a new company is likely to require much more time than a consulting agreement. They also question whether it is wise for graduate students to work on projects related to their thesis advisor's industrial interests, and whether commercialization may cause a shift in the nation's research from basic to applied biomedical research. Will graduate students receive a well rounded education if their graduate school experience is in applied research? Would they now choose industry over teaching and basic research? Would a shift from basic to applied biomedical research be in the country's best interests?

New biotechnology companies emerge every month, and each seeks to recruit the best possible staff. These companies are prepared to pay salaries much higher than the academic community. Thus commercialization is contributing to the phenomenon known as "brain drain." One writer has compared it to the American Indians' being forced to consume their seed corn, and therefore dooming the fate of the following year's crop (Science, July 10, 1981). If the university faculties are being recruited for industry jobs, who will remain to teach the next generation of scientists? The Harvard proposal and companies such as Ugen and DNA Science were designed to circumvent this problem. However, the Harvard proposal had problems which made it unacceptable to the faculty, and DNA Science has had preliminary troubles in starting up its new form of investment company. It remains to be seen whether companies such as Ugen and DNA Science will have an effect on the "brain drain" phenomenon.

One of the qualities which university researchers take pride in is their objectivity: the ability to be impartial when making statements on subjects of public interest. Recently, however, the credibility of university scientists associated with industry has fallen into question. During the Supreme Court hearing on the patentability of a genetically engineered microorganism, reference was made to Walter Gilbert's (Harvard/Biogen) views on the safety of recombinant DNA research. The United States Solicitor General argued that because of Dr. Gilbert's involvement with a biotechnology company, "he is thus hardly an impartial observer in the debate over the biohazards associated with genetic engineering" (Science, 1980, 208:688-692). (Dr. Gilbert has recently announced that he will resign from Harvard as of July 1, 1982, rather than relinquish his position in the company he helped found.)

A final objection, which also was a major topic in a recent (June 8, 9, 1981) congressional hearing, is whether the American public is indirectly funding industry by allowing the commercialization process to continue. Chairman Albert Gore of the House Subcommittee on Oversight and Investigations has asked if industry is "skimming off the cream produced by decades of taxpayer funded work." A case in point is the Massachusetts General Hospital (MGH) arrangement with Hoechst A.G., a West German chemical and pharmaceutical company. Hoechst agreed to pay MGH $50 million over the next 10 years and in return is receiving the first options rights for licenses from any projects which the company has funded. The licenses will be negotiated on a case by case basis, reflecting the financial contribution of the company to the specific patent being discussed. Hoechst cannot specify what type of work it would like MGH to perform, but it may refuse to support specific research projects. In addition, Hoechst is allowed to send individuals to MGH for training and consultation with the Hospital's faculty. The individual scientists at MGH will be allowed to publish when they choose, provided that hospital authorities are informed in advance. There will also be no restrictions on collaboration with other scientists. The MGH/Hoechst
contract was the subject of a General Accounting Office (GAO) investigation at the request of the House Science and Technology Investigations and Oversight Subcommittee. The GAO report indicates that it should be possible for MGH to separate research funded by Hoechst from federally funded research. According to the report, however, difficulties may arise when there is doubt over whether a patent exploited by Hoechst has been supported exclusively by the German company. In addition to the $50 million from Hoechst A.G., MGH is reportedly also receiving $15 million from two philanthropists, Arthur O. and Gullan M. Wellman, for the construction of new laboratory facilities.

Massachusetts General Hospital is not the only biomedical research facility with ties to industry. In addition to the funds Harvard is receiving from Monsanto, Dupont recently announced (June 1981) a $6 million grant for basic research in molecular genetics. The research will be directed by Philip Leder, formerly of NIH, who recently joined the Harvard Medical School as chairman of the newly formed Department of Genetics. The grant will be spread over a five year period with a $2 million payment in July 1981 and annual payments of $1 million through 1985.

Some further reported arrangements are as follows:

1) Phillips Petroleum invested $10 million in a joint venture with the Salk Institute to develop commercial applications of basic research from the Institute's laboratories.

2) The new French biotechnology company, Transgene, has distributed equity to the Pasteur Institute in Paris and to the University of Strasbourg. England's national biotechnology company, Celtech, will be sharing its profits and research results with the Medical Research Council Molecular Biology Laboratory at Cambridge.

3) At the University of Wisconsin, two scientists with research interests in agriculture have formed consulting/partnership associations with two biotechnology companies. Winston J. Brill is associated with Cetus, a firm near San Francisco which is in the process of setting up a Madison, Wisconsin, laboratory. Timothy C. Hall is working with Agrigenetics.

4) Several members of the molecular biology and microbiology department at Tufts University medical school have formed a research consulting partnership separate from the University.

5) The University of California, Davis signed an agreement with Allied Chemical for a $2.5 million grant over the next five years. Raymond C. Valentine, a plant geneticist at Davis, played an instrumental role in the contract negotiations which lasted for about two years. While the negotiations were taking place, Valentine proceeded to form a non-profit institution called Cal Gene which was eventually transformed into Calgene, a private corporation. Shortly after the grant negotiations were finalized, Allied announced that it had purchased a 20% equity interest in Calgene. To avoid possible charges of conflict of interest, Valentine agreed to cease his involvement with the University's $2.5 million grant. A University committee is in the process of preparing a detailed set of recommendations, to be released in June, defining University-industry interactions.

6) Washington University in St. Louis and Mallinckrodt Inc., a chemical manufacturer, have signed a $3.88 million agreement for genetic research. The research involves the production of monoclonal antibodies from...
artificially created cells called hybridomas. Mallinckrodt will have the option to license results from research it sponsors and will pay royalties to the University. The scientists will be free to publish their research findings and to exchange new cell lines and antibodies with outside scientists. Washington University has also signed a $1.8 million agreement with Monsanto Corp. to produce monoclonal antibodies.

(7) The Massachusetts Institute of Technology (MIT) accepted (12/4/81) a gift of $7.5 million and $120 million for the establishment of the Whitehead Institute for Biological Research. Nobel laureate David Baltimore will become the Institute's director while continuing as a professor of Biology at MIT. The money for both gifts was donated by Edwin C. Whitehead of Connecticut who recently sold Technicon, a company he founded in 1939, to Revlon for $400 million.

(8) Yale University and Celanese Corporation, a chemical manufacturer, announced the signing of a three-year $1.1 million research contract on Feb. 17, 1982. Celanese is interested in learning how to use naturally occurring enzymes in the manufacture of chemicals and fabric. Yale has also formed an Office of Cooperative Research in an effort to tighten ties between the University and corporations.

(9) The Alberta Research Council, an agency of Alberta province, has signed a 4-year, $8 million agreement with Biologicals, Inc. for the use of enzymes in industrial applications. Work on the project will be conducted on the campus of the University of Alberta in Edmonton.

(10) Dr. Herbert Boyer, director and vice president of Genentech, a genetic engineering company, still retains his faculty position at the University of California, San Francisco.

(11) Cold Spring Harbor Laboratories, directed by Dr. James Watson, is in the process of setting up a corporation which will help commercialize the laboratories' scientific discoveries. The corporation will operate separately from the Laboratory.

(12) The University of California at Berkeley, Stanford, and Engenics, a biotechnology concern, have received financial backing from six major corporations: General Foods Corp.; Bendix Corp.; Elf Technologies unit of Societe Nationale, Elf Aquitaine; Koppers Corp.; Mead Corp.; and Maclaren Power and Paper Co., a subsidiary of Noranda, Mines Ltd. The universities' shares of the research funding will be channeled through a new cooperative nonprofit center for biotechnology research. The center will hold a 30% equity share of Engenics and will channel any capital appreciation or stock dividends from the new company back into basic research at the two universities. The universities will cooperate in research with Engenics, which received $7.5 million from the six corporations.

(13) Johns Hopkins University and Hybritech, a San Diego biotechnology firm, signed an agreement Feb. 12, 1982, to develop and evaluate radioactive antibodies for cancer treatment. Hybritech will provide the antibodies which Hopkins' oncology center will use in clinical trials.

(14) The Rockefeller University and Monsanto Co. have announced (March 1982) a five-year $4 million agreement under which Monsanto will support basic research in plant molecular biology at the University.

(15) Dupont and the University of Maryland have an agreement to produce
interferon in Bacillus subtilis, a non-pathogenic soil bacterium.

(16) FMC Corporation has given (June 1981) Frederick M. Ausubel of Harvard University $190,000 for each of the next 3 years for research on nitrogen fixation in plants.

(17) A.M. Chakrabarty of the University of Illinois has agreed to a 2-year contract with Petrogen for the development of genetically engineered bacteria for enhanced oil recovery.

(18) Monsanto Co. and Washington University announced on June 3, 1982, a $23.5 million 5-year biomedical research contract for study of the breakdown of genetic functions and cell communication associated with several diseases.

Universities are beginning to set up their own conflict-of-interest-rules. The University of California, Davis, mentioned above, is one example. In late September 1981, the faculty council of Harvard University agreed to recommend to the full faculty a new set of procedures which would establish the "Faculty Committee on Conflicts of Interest." If adopted, the new rules would require that faculty members notify the Conflicts of Interest Committee about any outside commitments. The rules would also limit such commitments to 20% of the faculty member's time. Stanford University already has a formal set of guidelines due to its faculty's involvement with the microelectronics industry. However, Stanford is in the process of developing new proposals to tighten up the existing guidelines. In addition, on Mar. 27, 1982, the presidents of five leading U.S. universities (Stanford, Harvard MIT, California Institute of Technology, and the University of California system) attended a conference in Watsonville, California, with scientists and business leaders on the commercial use of university scientific research. The conference produced a 10-page statement containing recommendations for universities that have recently developed relations with industry. Meanwhile, the House Science and Technology Investigations and Oversight Subcommittee has asked the National Academy of Sciences and the American Association of Universities to draft a code of ethics for financial arrangements between universities and industry.

LEGISLATION

P.L. 97-34, H.R. 4242


H.R. 1937 (Kastenmeier)

Amends the patent law to extend the term of patents which encompass specified products over a method for using a product any of which are subject to certain nonpatent regulatory review periods. Introduced Feb. 18, 1981; referred to Committee on Judiciary.

H.R. 4326 (LaFalce)

Amends the Small Business Act to require Federal agencies to establish small business innovation research (SBIR) programs. Introduced July 29,

H.R. 5919 (Waxman)

Amends the Public Health Service Act to revise and extend the authorities under that Act relating to national research institutes. Also, requests a report from the Institute of Medicine on the effects of commercialization on biomedical research. Introduced Mar. 22, 1982; referred to Committee on Energy and Commerce.

S. 255 (Mathias et al.)

Amends the patent law to extend the terms of patents which encompass specified products or a method of using a product, any of which are subject to certain nonpatent regulatory review periods. Introduced Jan. 27, 1981; referred to Committee on the Judiciary. Reported (S.Rept. 97-138) June 16, 1981; passed Senate amended July 9, 1981; referred to House Committee on the Judiciary July 13, 1981.

S. 881 (Rudman et al.)


HEARINGS


on Science, Research and Technology. Commercialization of academic biomedical research.


CHRONOLOGY OF EVENTS

03/27/82 -- The presidents of five leading U.S. universities (Stanford, Harvard, MIT, California Institute of Technology, and the University of California system) attended a conference in Watsonville, California, with scientists and business leaders on the commercial use of university scientific research.

01/06/82 -- The American Association for the Advancement of Science (AAAS) held a session entitled "Commercial Genetic Engineering: Impacts on Universities and Nonprofit Institutions."

12/04/81 -- Massachusetts Institute of Technology (MIT) accepted gifts of $7.5 million and $120 million from E.C. Whitehead for the establishment of the Whitehead Institute for Biological Research.

10/16/81 -- The General Accounting Office published a legal analysis of the research contract between Massachusetts General Hospital and Hoechst A.G., a West German chemical company.

08/13/81 -- H.R. 4242, the Economic Recovery Tax Act, was signed into law (P.L. 97-34). Allows tax credits for basic research.

07/10/81 -- The editorial "The fate of the seed corn" appeared in Science. Highlighted the impact of losing experienced university professors to the biotechnology industry.

06/29/81 -- Dupont announced a $6 million grant to Harvard Medical School in support of basic research in molecular genetics.

06/08-09/81 -- House Science and Technology Subcommittee on Investigations and Oversight and Subcommittee on Science, Research and Technology held hearings on the "Commercialization of Academic Biomedical Research."
06/08/81 -- The advisory committee to the director of NIH held a meeting which discussed whether the quality of basic research is compromised by industrial support.

05/20/81 -- The West German Chemical firm, Hoechst A.G., announced a $50 million grant to Massachusetts General Hospital to support basic research in molecular genetics.

12/12/80 -- H.R. 6933, the Patent and Trademark Amendment Act was enacted (P.L. 96-517), providing a new policy for the allocation of patent rights resulting from federally-supported research.

11/17/80 -- Harvard President Derek Bok announced that Harvard University would not become involved in a new genetic engineering company.

02/00/75 -- Monsanto announced a $25 million grant to Harvard University in support of investigations in molecular biology.

ADDITIONAL REFERENCE SOURCES


