Thackeray ↓

DRAFT

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Private knowledge and public policy:
The rise of the American biotechnology industry

As the pages of Science and other professional journals attest, in the 1990s it is difficult to find a molecular biologist who does not have a financial stake in marketing biotechnology.[1] We here propose a study that will explore the meaning of this professional reality for the community of practicing molecular biologists. How have corporate interests shaped their work? And how have public policies and institutional constraints affected their choices? Most importantly, what can this story tell us about knowledge as property?

Our study of post-Asilomar molecular biology will focus on the changing cultural and economic meaning of the knowledge produced by this scientific field. Examining how American science policy has shaped the shifting relationships between molecular biologists and private industry, we will place this very recent story in a larger context. We will relate contemporary private science to the history of biotechnology in general, and to the history of academic-industrial relations. We hope to show how the culture of molecular biology has been affected by the

increasing capitalization of the knowledge produced by the field, and to thereby suggest some of the implications of a more general quality of contemporary science, that is, its role as intellectual property.

Background

While it is possible to interpret ancient beer-brewing as the beginning of biotechnology, we date the beginning of molecular biotech in 1971. Paul Berg at Stanford was developing plans to implant DNA from Simian Virus 40 in the bacterium e. coli. E. coli normally inhabits the human digestive tract. Berg's graduate student Janet Mertz mentioned Berg's plan to Robert Pollack, who was then teaching a seminar on safety and ethics in working with mammalian cell cultures, at Cold Spring Harbor Laboratory, New York. Pollack began to wonder if the SV40 virus, believed to be harmless to human beings, might become a problem if introduced into the human digestive tract through e. coli. At first, Berg dismissed Pollack's concerns. But when he consulted other scientists, including Maxine Singer and David Baltimore, he found that they too were critical of his plans. Berg decided to bring up the question in a 1972 lecture at the European Molecular Biology Organization, but the resulting discussion did not clarify the problems. Berg decided not to proceed with the experiment--partly because he thought

the virus would not be expressed in e.coli.[2]

Berg's tentative plan and the open discussion it provoked set off a worldwide debate. By November 1972, the U.S. National Institutes of Health had established a biohazards committee, and the U.S. National Institute of Allergies and Infectious Disease had developed a policy for the handling of virus samples. In January 1973, Berg organized the first Asilomar Conference, held at the Asilomar Conference Center, Pacific Grove, California. The scientists involved, then, created the controversy over recombinant DNA. The debate focused on hazards that had not yet been demonstrated, and on practices that had not yet been widely used. The scientists involved were expressing their fears--labeled by Nobelist James Watson as "mysticism"--that they did not understand how viruses worked, and they could not be sure that the new combinations would not be disastrous.

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The feared manipulation of DNA became a reality with the development of a plasmid that would maintain its replication functions even with inserted DNA in (November 1973)[3]. Meanwhile, the scientists continued their high-profile, public debate. The "Berg Letter," published in July 1974, asked scientists to defer further experiments until the hazards could be evaluated. At the same time, the biomedical research community organized an extensive effort to promote genetic engineering research based on the

idea that "new evidence" showed that recombinant DNA was not hazardous. Relaxation of some guidelines in the early 1980s provoked an increase in both corporate and NIH funding for recombinant DNA research. And patent and tax policies of both the Carter and the Reagan administrations encouraged joint university-industry research, particularly by permitting universities to patent the results of research funded by the federal government. (Wright, 1993, 95).

At the same time, the commercial development of this apparently dangerous new technology began to seem more likely. Genentech, the first American firm to exploit recombinant DNA technology, was founded in 1976. In 1980, Genentech's initial public offering set a Wall Street record for the fastest price per share increase (from $35 to $89 in 20 minutes). Supported by U.S. tax laws and by the availability of venture capital, other new biotechnology firms rapidly followed Genentech's example. By the mid 1980s, many academic scientists were forming their own companies, or agreeing to license their findings to established biotech firms. The 1980 Supreme Court ruling in Diamond v. Chakrabaty, that microorganisms could be patented, facilitated this rush to develop the biotech industry. In the following year, 80 new biotechnology firms were created.

Just as scientists and entrepreneurs began trying to

make sense of the new molecular biotechnology, so too did science policy analysts, political leaders and the public. On 23 June 1976, in the midst of a lively public debate on college campuses, in some municipalities and in some state legislatures, the NIH issued guidelines for recombinant DNA research. The NIH guidelines were grounded in four basic assumptions about recombinant DNA research. First, some experiments were so hazardous they should not be done at all. Second, others could be undertaken if appropriate safeguards were in place. Third, the level of containment should match the estimated potential hazard of the work. And fourth, the guidelines should be subject to regular review and revision as changing scientific data permitted new assessments of risk. The guidelines were not "regulations," and in any case they applied only to research funded by the NIH. This meant that a good deal of recombinant DNA research could proceed unrestricted by controls or limits in institutions that did not receive NIH funding--most conspicuously, in the laboratories of private industry. (Russell, 82-83)[4]

The NIH appealed to the Pharmaceutical Manufacturer's Association for voluntary compliance just as the guidelines were completed, but the response was unenthusiastic. A spokesman for Upjohn said he feared that limits on corporate recombinant DNA research would be "the first step of another wave of bureaucratic intervention" into private

industry. An Eli Lilly spokesman said the company had a lot of experience with hazardous work, and while it would consider the guidelines when appropriate, it would ignore them if "we feel . . we are capable of guaranteeing the safety of the exercise in question." (Russell, 83-84)

The first efforts to regulate the new techniques, then, were of mixed efficacy. The 1976 guidelines did create an oversight structure--forms for grant applicants, a system of reporting and assessing, and so on. But their impact on recombinant DNA research was inherently limited, most conspicuously by the fact that industrial cooperation was voluntary. Indeed, industrial compliance continues to be voluntary and informal. The Office of Technology Assessment has stressed that private firms would find it much more difficult to fight private legal action should any accident occur, if it could be shown that the corporate laboratory did not follow the NIH guidelines. In effect, the guidelines are the standard against which negligence can be measured. But there are no penalties per se for industrial violations of the guidelines, and the U.S. system, in a laissez-faire manner, encourages the use of new biotechnologies by private companies.

The boom years

In the 1980s, in an expanding economy and with few legislative constraints, American biotechnology took off.

Genentech, founded in 1976 by venture capitalist Robert Swanson and biochemist Herbert Boyer, released the first recombinant DNA drug, human insulin, in 1982. Three years later Genentech introduced a synthetic human growth hormone for children with growth hormone inadequacy. In 1986, the Food and Drug Administration approved the use of the first human hepatitis vaccine made with recombinant DNA methods. Meanwhile many companies began field testing genetically altered bacteria for various agricultural uses; and the first human gene therapy trials were approved in September 1990.[5]

Much of this growth was driven by changes in patent protection standards that made it possible for "products of nature" to be patended. In the Diamond v. Chakrabarty case in 1980, the Supreme Court ruled that a bacterium genetically engineered to break down crude oil was a "manufacture" and could therefore be patented. Before this case, the U.S. Patent and Trademark Office had maintained that microorganisms could not be patented. But the decision in Diamond v. Chakrabarty drew on existing legislation, particularly the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970, to rule that living organisms could be intellectual property.

In the 1980s, Congress reinforced the Supreme Court's ruling by amending patent law to permit small businesses and nonprofit organizations to keep the rights to

inventions developed with federal funding, and to permit federal grantees to transfer their patent rights to private firms. While providing the biotechnology industry with an economic boost, these new patent laws also led to much litigation over infringement.

In 1988, the first animal patent was granted to Harvard University for mouse engineered to be exceptionally susceptible to cancer. This transgenic mouse was the focus of a public controversy. Researchers in both academia and industry defended the patent ruling, arguing that such organisms promised unique medical and agricultural benefits and deserved patent protection. But opponents of animal patenting maintained that it would hurt small farmers, violate a moral obligation to preserve the integrity of species, and lead to decreased scientific communication as researchers tried to protect their investments. Patenting controversies have continued to play a role in biotechnology policy and the public discourse, more recently with the attempt by the National Institutes of Health to patent fragments of genes before the genes had been isolated or characterized.

While the biotechnology industry was exploding in the mid 1980s, several molecular biologists were proposing to create a public database that would serve a wide constituency. Their goal was a complete map of the human genome, and they began their project with the expectation

that it would be of little interest to private industry. The map would help researchers looking for genes, its promoters said, and could lead to more and better genetic therapies. The human genome project formally began in 1987, and venture capitalists were not interested. But by 1993, they were key players, matching the federal government's $170 million budget for genomics research with about $90 million in private funds. One journalist in Science observed that what was "heresy" when HGP began--that the genome should be mapped by private industry--had become "dogma."[6]

While the relationships between HGP researchers and private industry are now the focus of some public controversy, they are not only legal but have been encouraged by federal science policy. The American regulatory and court system minimized limitations on genetic engineering, promoted liberal patent rights for the products of biotechnology, permitted academic scientists to license the products of research conducted with public funds and approved gene therapy trials despite significant uncertainties about the effectiveness of the therapies. While the industry itself has complained a good deal about overregulation by the Food and Drug Administration, the Environmental Protection Agency and the U.S. Department of Agriculture, American regulation has been relatively tolerant when compared to that of other countries. In

economic terms, these policies paid off: By the end of 1992, more than 1,200 biotechnology companies employed 79,000 people, spent an annual $5 billion on research and realized almost $6 billion in sales. More than 600 biotech diagnostic products were on the market, as were 20 biotechnology therapeutics. More than 150 biotech therapeutics were in clinical testing, and an estimated 2,400 product license applications were pending at the FDA's Center for Biologics Evaluation and Review.[7] The biotech industry, despite a dismal 1992 that some analysts have blamed on patent litigation, is commonly seen as one of the most promising growth sector's in the U.S. economy. Many of those who are being and will be absorbed into this growing industry are trained molecular biologists.

The molecular community

While there have been many studies of the biotechnology industry, and of biotechnology policy, the impact of these events on the culture of molecular biology has received little attention. In a 1985 paper, sociologists Markle and Robin attempted a predictive assessment of this impact. "It seems to us that the demands of biotechnology will alter basic science with a subtlety that will be difficult to perceive." They suggested that one manifestation of this alteration might be found in the language used to describe biotechnology and

molecular biology, the invocation of "basic research" in corporate promotional materials, for example. The new biotech could also transform academic goals, so that "publish or perish" will be replaced by "profit or perish."[8] They pointed out that an OTA survey in 1984 found that 85 percent of university researchers polled believed that "university/industry relations have had no effect on the way research is done" or on the "exchange of information" in science. And 50 percent believed that the quality of education had been enhanced by these relationships.[9] "Even if this optimistic, probiotechnology scenario were true," they noted, "molecular biology would advance in noncommercial areas only if the basic science agenda were not .... altered by biotechnology" a possibility they described as "remote."[10] Conversely, critics of the new biotechnology have predicted that it will lead to the subordination of research to commerce.(Markle and Robin, 76).

For young molecular biologists, the corporate world has become an attractive career option, particularly in the form of a period of post-doctoral research at one of the major biotechnology firms. A recent survey by the Industrial Biotechnology Association found that 90 percent of biotech firms offer post-doctoral training. Genentech's program is large and highly competitive--the company turns away nine candidates for every one it accepts--and those at

Eli Lilly and Pfizer are also widely respected.[11]

Thus the rise of the biotech industry has already begun to shape career paths, priorities and expectations among molecular biologists. In 1993, it now seems possible to focus a serious study on this question, not in quantitative but in qualitative terms.

Research plan

We seek funding for a post-doctoral researcher for three years of research and writing. The post-doc will conduct 40 oral history interviews with selected scientists (see list, appendix A). [Betsy: We need to start keeping a file on scientists who could be interviewed. We have a list from the NIH application, but we should be expanding it] The post-doc will also plan, organize and conduct five round-table discussions with leading individuals in the biotech industry (see participant list, appendix B). Both the round-table discussions and the oral histories will be transcribed and made available to other researchers at the Beckman Center archives, as a part of the center's oral history collection. And we will sponsor two academic conferences to keep in touch with the community of students of science who are working on related and relevant topics.

We seek funding for salary and benefits for this post-doctoral researcher for three years; travel and expenses; funding for conducting and transcribing the oral histories

and round tables; and support for the conferences. The center will provide an office, computer and clerical support to the post-doctoral researcher.

This project will be coordinated with the Center's archival documentation study of the Human Genome Project. We see these two projects as complementary, and hope that the insights of the post-doc will help inform the archivist's work, and that the archivist's findings will help the post-doc.

We are clearly choosing a topic with manifest difficulties of documentation and access, but wish to argue that difficulty of access should not preclude historical attention. The documentation of sixteenth century popular culture in Italy is no less problematic than the documentation of contemporary molecular biology and the biotech industry--in volume, at least, the contemporary records are far superior. And while there may be some details to which we cannot gain access by the means we propose (use of public records, interviews, use of whatever corporate records we can acquire) we want to suggest that it is still worth asking the questions and trying to get the answers. This is particularly true given the policy and economic implications of the events we are exploring.

The book resulting from this study, tentatively entitled Private science and public policy, will explore the rise of the biotech industry and its impact on the

mores and culture of molecular biology. We are particularly interested in how scientists have interpreted the transformation of their field. The book will explore several related questions. A rough outline is as follows:

1. Asilomar I and II. Why did scientists such as Berg react to rDNA with so much anxiety? What was the real threat posed by recombinant techniques? How did the culture of Asilomar set the stage for the later transformation of molecular biology?

2. The invention of molecular biotechnology. The venture capitalists were intrigued by the pageantry of Asilomar--it may have drawn them to molecular biologists.

3. New relationships: How was the early scientific-corporate axis negotiated? How did the agreements work? What did the scientists interpret as their priorities? What demands did the entrepreneurs make?

4. The boom years: 1980-1985. The stage was set for the rise of highly capitalized biotech industry. A court ruling legitimized the plans, and Genentech and Cetus both set Wall Street records. Did this public financial frenzy influence working scientists? Did it shape how they thought about their work? How did its impact appear?

5. Inventing HGP: originally intended as strictly an academic endeavor, HGP quickly became a corporate arena--issues of proprietary information and possible gene therapies, patenting DNA--for scientists, a dizzying

change, directed research gone mad? Are these agendas simply impossible? E.G. Map the chromosome as per NIH, patent to please the corporate sponsor, work freely and share data but also conceal, protect. The HGP institutionalizes these tensions over the proper distribution of knowledge.

6. Conflict of interest: Reconstructing community norms. In the late 1980s and early 1990s, scientists began to rethink ideas about conflict of interest and full disclosure. What assumptions guided their debates? How does the conflict of interest debate--which led to James Watson's resignation as head of NCHGR--shed light on the changing culture of molecular biology? Is there a pattern of noisy public debate followed rapidly by acceptance within the scientific community? Are there resisters in the community?

7. Building science policy: How can the economic interests of a science best be served? What does the applied v. basic debate mean in contemporary science? What uses does it serve? What does this history tell us about contemporary science and scientists?

8. Conclusions.

Our goal is to explore the role of American science policy in the transformation of molecular biology. Through interviews, public records and participant observation, we will reconstruct the intellectual, technological and

cultural metamorphosis of the field of molecular biology, 1972-1992. Our subject will be the scientists in context, as economic and intellectual actors, dealing with the rapidly changing social and intellectual mores of their field. How has the capital value of the knowledge produced affected scientific practice? Scientific communication? How has it shaped the culture of professionalism in the field?

We will draw on the existing literature on biotechnology policy but focus our attention on the culture of molecular biologists rather the culture of policy analysts. We want to see the shifting meaning of this science from the perspective of those creating the knowledge.

That many molecular biologists feel threatened by the shifting economic meaning of their work is suggested by a recent program of the American Society of Cell Biology proposing to use history to prove the value of basic research. ASCB president Susan A. Gerbi is soliciting "scholarly historical accounts of the process of discovery" in the hopes that such accounts will demonstrate that "federal investment in fundamental, untargeted biological research will have future pay-offs in unforeseen applications that will better the health of our citizens and the economy of our country."[12] But in practice much of the research identified by practitioners as "basic" was

focused on solving problems with economic and medical implications. The Polymerase Chain Reaction, PCR, for example, cited in the ASCB literature as a form of basic research, was developed by a scientist employed in private industry (Kary Mullis, then at Cetus) and intended to facilitate the commercialization of gene therapy.[13] The development of tetracycline was part of a focused corporate effort to discover better antibiotics. And the "basic research on viruses that infect chickens" focused on a widespread agricultural problem with economic implications.

While our attention will focus on the last twenty years, we want to place this very recent history in historical context, to show that it is a manifestation of a long, slow change in the cultural meaning of science, and to suggest that it has important implications for the public management of science.

End notes

1. See, for example, Science 31 July 1992 "Conflicts of Interest" report, 616-626.

2. See Allan M. Russell The Biotechnology Revolution 40-43; also C. Grobstein A Double Image of the Double Helix: The Recombinant DNA Debate (W.H. Freeman: San Francisco: 1979); June Goodfield Playing God (Hutchinson: London, 1977); Nicholas Wade The Ultimate Experiment: Man-Made Evolution (Walker and Company, New York, 1977).

3. S.N. Cohen et al "Construction of Biologically Functional Bacterial plasmids in vitro" Proceedings of the National Academy of Sciences Vol. 70, No. 11, November 1973 3240-3244.

4. Russell, 64-65.

5. Steven A. Roseberg received permission from the Recombinant DNA Advisory Committee advising the NIH to use gene altered white cells in the treatment of melanoma. See "Human Gene Therapy Wins Crucial Victory" Science News 9no date?0 als, Wills, 230-231.

6. See Christopher Anderson "Genome Project Goes Commercial" Science v. 259, 15 January 1993, 300-302.

7. See Ernst and Young "Biotech '93: Accelerating Commercialization" [BETSY: CAN STEPHANI ORDER THIS REPORT FOR US?)

8. Gerald E. Markle and Stanley S. Robin "Biotechnology and the Social Reconstruction of Molecular Biotechnology"

Science, Technology and Human Values Winter 1985 10:1, 70-79.

9. Office of Technology Assessment Commercial Biotechnology: An International Analysis (Washington D.C., U.S. Government Printing Office, 1984).

10. Markle and Robin, 76.

11. Jean Wallace "More biotech PhD's are opting to take postdocs in industry" The Scientist 12 October 1992.

12. Susan A. Gerbi, President, ASCB, to Rosemary Stevens, 27 January 1993, describing the professional group's interest in commissioning some short historical accounts of major discoveries with unexpected practical applications.

13. Get a citation to Mullis paper? What is the date?