Making Dollars Out of DNA

The First Major Patent in Biotechnology and the Commercialization of Molecular Biology, 1974–1980

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ABSTRACT

In 1973–1974 Stanley N. Cohen of Stanford and Herbert W. Boyer of the University of California, San Francisco, developed a laboratory process for joining and replicating DNA from different species. In 1974 Stanford and UC applied for a patent on the recombinant DNA process; the U.S. Patent Office granted it in 1980. This essay describes how the patenting procedure was shaped by the concurrent recombinant DNA controversy, tension over the commercialization of academic biology, governmental deliberations over the regulation of genetic engineering research, and national expectations for high technology as a boost to the American economy. The essay concludes with a discussion of the patent as a turning point in the commercialization of molecular biology and a harbinger of the social and ethical issues associated with biotechnology today.

ON 2 DECEMBER 1980 THE U.S. PATENT OFFICE issued the first major patent in the new biotechnology, one of three patents subsequently known as the Cohen-Boyer recombinant DNA cloning patents.[1] The first patent is based on the 1973–1974 development by Stanley N. Cohen of Stanford and Herbert W. Boyer of the University of California, San Francisco (UCSF), of a fundamental process of molecular biology that came

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[1] Stanley N. Cohen and Herbert W. Boyer, "Process for Producing Biologically Functional Molecular Chimeras," United States Patent 4,237,224, 2 Dec. 1980. As Robert Bud has illustrated, industry based on biotechnology, broadly described as the use of living organisms for commercial purposes, is ancient: Bud, *The Uses of Life: A History of Biotechnology* (Cambridge: Cambridge Univ. Press, 1993). Although I recognize that the present science and industry of biotechnology have antecedents, in this essay I use "biotechnology" in the more recent and narrower sense of a science and industry based on the manipulation of DNA.

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to be known as recombinant DNA technology.[2] The concept arose in November 1972 as the two scientists brainstormed on a late-evening walk after attending a scientific conference in Hawaii. Sketching out a research collaboration over deli sandwiches, Cohen and Boyer agreed to pool their respective expertise in plasmid biology and bacterial restriction enzymes in experiments that they began soon after returning to the mainland. By March 1973, at most four months after initiating the experiments, Cohen, Boyer, and their coworkers at Stanford and UCSF knew that their DNA splicing and cloning (amplifying) procedure worked. In November they published a paper entitled "Construction of Biologically Functional Bacterial Plasmids *In Vitro*." Years later, Boyer recalled his emotions at the instant of success: "I think the most exciting moment was when we did the first experiments with the recombined plasmid DNA. [Colleague] Bob Helling and I looked at the first [electrophoresis] gels, and I can remember tears coming to my eyes, it was so nice. I mean, there it was. You could visualize your results in physical terms, and after that we knew we could do a lot of things."[3]

What became apparent as recombinant DNA technology was rapidly adopted in molecular biology laboratories around the world was that it could indeed "do a lot of things." It gave scientists a simple method for isolating and amplifying any gene or DNA segment and moving it with controlled precision, allowing analysis of gene structure and function in simple and complex organisms.[4] The process was revolutionary for molecular biology. But it was more than that: it was soon found to have great potential in commercial applications as well. In November 1974 Stanford and the University of California (UC) applied for a patent on recombinant DNA. What was expected to be a routine patent application turned into a six-year ordeal. The history of the effort to secure the patent has never been told in detail. There are two existing accounts, a cursory three-page paper by Stanley Cohen and a somewhat longer paper by Niels Reimers, who as director of Stanford's Office of Technology Licensing (OTL) managed the patenting and licensing of the Cohen-Boyer invention. Both are narrow, virtually unreferenced accounts written for scientific or technical audiences.[5]

[2] Cohen and colleagues introduced the term "recombinant DNA" in early 1974, intending it to be synonymous with DNA cloning. The term is also used in a narrower sense to refer only to the composite molecules that result from the joining of DNA fragments in a test tube. See Stanley Cohen's presentation on "The Science" at a conference entitled "The Emergence of Biotechnology: DNA to Genentech," sponsored by the Chemical Heritage Foundation, Philadelphia, 13 June 1997, transcripts, pp. 23–32, on p. 23. The wider meaning of "recombinant DNA" and "recombinant DNA technology" is intended in this essay. The process consists of isolating and inserting a gene or segment of DNA into a plasmid (a circle of DNA found in bacteria) and transferring the "recombinant" DNA to bacteria, where it is reproduced or "cloned" in identical genetic copies. The foreign gene can be transcribed and expressed in the bacteria as a protein, such as a hormone.

[3] Stanley N. Cohen, Annie C. Y. Chang, Herbert W. Boyer, and Robert B. Helling, "Construction of Biologically Functional Bacterial Plasmids *In Vitro*," *Proceedings of the National Academy of Sciences, USA,* 1973, *70:*3240–3244; and Herbert W. Boyer, interview by Sally Smith Hughes, 28 Mar. 1994, draft, p. 56. (Interviews with Boyer cited in this essay are steps toward an oral history, as yet incomplete.) For a contemporary account of the splicing and cloning procedure see Cohen, "The Manipulation of Genes," *Scientific American,* 1975, *233:*24–33.

[4] One indication of the speed with which the recombinant DNA method was adopted in science is Stanley Cohen's list, dated September 1974, of the names of the thirty-two recipients of his plasmid, pSC101, at the time the only vector or vehicle available for transfer of the selected DNA segment into bacteria for cloning. Stanley N. Cohen to Dick Roblin, 5 Sept. 1974, Cohen Personal Correspondence, Biohazard Collection, Stanford Univ., Stanford, California. For contemporary accounts of the technical usefulness and early applications of recombinant DNA in basic research see Jean L. Marx, "Molecular Cloning: Powerful Tool for Studying Genes," *Science,* 1976, *191:*1160–1162; Bob Williamson, "First Mammalian Results with Genetic Recombinants," *Nature,* 1976, *260:*189–190; and Eleanor Lawrence, "Nuts and Bolts of Genetic Engineering," *ibid., 263:*726–727.

[5] Stanley N. Cohen, "The Stanford DNA Cloning Patent," in *From Genetic Engineering to Biotechnology—*

A full history of the patent merits telling, not least because of its importance as a turning point in the commercialization of molecular biology. Historians have emphasized the continuities between modern DNA-based biotechnology and previous commercially oriented biological research that likewise had industry sponsorship and proposed to use science to manipulate living organisms for commercial purposes.[6] While I agree that some continuities exist, commercial activity in molecular biology was until recently episodic and generally unrepresentative of a discipline overwhelmingly focused on basic problems. With its sweeping claims on the recombinant DNA process, the patent became an agent in the transformation of molecular biology from a predominantly academic discipline to one with pervasive practical applications and industry connections. This patent history sets the stage for a shift in attitude and research emphasis in molecular biology in the 1980s toward a focus on applications, extensive interaction with the commercial world, and a resultant blurring of boundaries between academia and industry.[7]

Three sets of actors—universities and academic scientists, government officials, and entrepreneurs and established corporations—followed the course of the Cohen-Boyer patent application, watching for clues to the future of recombinant DNA as an industrial process. But in addition to the patent's status as first a barometer and then a landmark of commercial biotechnology, its history has its own intrinsic significance. It was played out during a critical period of debate in the 1970s about the role of science and technology in the national economy. Who should benefit from public support of academic science? Should science and technology be regulated and constrained? If so, how and by whom? These questions were being discussed in many areas of science and technology in the 1970s, but nowhere with more heat and publicity than in the controversy over the research and development of recombinant DNA.[8] The effort to patent this breakthrough in molecular science and technology became a major focus in the debate.

In this essay I detail the six years of concerted effort by Stanford to obtain a patent on the Cohen-Boyer process and describe its relationship to the politics of the recombinant DNA controversy and shifts in national policy and priorities. Early anxieties over the social

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The Critical Transition, ed. W. J. Whelan and Sandra Black (New York: Wiley, 1982), pp. 213–216; and Niels Reimers, "Tiger by the Tail," *Chemtech*, Aug. 1987, pp. 464–471. Cohen's paper references only the patent, and the two references in Reimers's article, probably added by an editor, are to previously published articles in *Chemtech* on patenting in biotechnology.

[6] Angela Creager, "Biotechnology and Blood: Edwin Cohn's Plasma Fractionation Project, 1940–1953," in *Private Science: Biotechnology and the Rise of the Molecular Sciences*, ed. Arnold Thackray (Philadelphia: Univ. Pennsylvania Press, 1998), pp. 39–62; Lily Kay, *The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology* (New York: Oxford Univ. Press, 1993); Jean-Paul Gaudillière, "The Molecularization of Cancer Etiology in the Postwar United States: Instruments, Politics, and Management," in *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s–1970s*," ed. Soraya de Chaderevian and Harmke Kamminga (Amsterdam: Harwood, 1998), pp. 139–170; and Nicholas Rasmussen, "The Forgotten Promise of Thiamin: Merck, Caltech Biologists, and Plant Hormones in a 1930s Biotechnology Project," *Journal of the History of Biology*, 1999, *32*:245–261.

[7] Almost simultaneous with the patenting of the Cohen-Boyer procedure was Cesar Milstein and Georges Kohler's development and publication in 1975 of the monoclonal antibody/hybridoma technique. For an ethnography of its path from discovery to commercialization, which took a different course from the Cohen-Boyer method, see Alberto Cambrosio and Peter Keating, *Exquisite Specificity: The Monoclonal Antibody Revolution* (New York: Oxford Univ. Press, 1995).

[8] The regulation of recombinant DNA research and the complex politics surrounding it have been documented by a number of authors. See, e.g., Susan Wright, "Recombinant DNA Technology and Its Social Transformation, 1972–1982," *Osiris*, 2nd Ser., 1986, *2*:303–360; Wright, *Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972–1982* (Chicago: Univ. Chicago Press, 1994); Sheldon Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (Cambridge, Mass.: MIT Press, 1985); and Herbert Gottweis, *Governing Molecules: The Discursive Politics of Genetic Engineering in Europe and the United States* (Cambridge, Mass.: MIT Press, 1998).

and environmental implications of science and technology and their commercial development, while they did not altogether disappear, were overwhelmed by the economic concerns and pro-business policies that came to the forefront in the late 1970s. The Carter and Reagan administrations turned to high-technology areas such as semiconductors and recombinant DNA for help in restoring the nation's technological leadership and economic strength. Yet this transition was neither simple nor seamless, particularly for universities and their science faculties. Professors and institutions had to reconcile traditional academic ideals with the quest for commercial profit in biology. Could universities and their scientists maintain the tradition of free and disinterested academic inquiry when confronted with the pressures of the marketplace? Would patenting and other forms of commercial activity in academia blemish the image of the university as a bastion of pure research, education, and public service? Who, in short, should own and control and profit from scientific knowledge?

The patent history, encompassing these wider issues, provides fresh insight into the national and academic debates over science and technology policy in the 1970s and the broader economic and political contexts in which biomedical scientists and institutions shifted from ambivalence about to acceptance of commercial science and technology. I will argue that the patent set legal precedent and provided reassurance at a critical moment in the movement toward extensive commercialization of recombinant DNA and other molecular technologies. In so doing, it served as an agent and symbol of institutional and attitudinal change that encouraged American universities and business interests to become more actively involved in the commercial exploitation of basic biomedical research, particularly in molecular biology.

STANFORD CONSIDERS A PATENT APPLICATION

A front-page story in the 20 May 1974 edition of the *New York Times* provoked Stanford's interest in applying for a patent on the Cohen-Boyer cloning method. The article, by Victor McElheny, covered research that Cohen, Boyer, and their collaborators had just published on the cloning of genes of a higher organism, the South African clawed frog. The work represented an exciting extension of two earlier publications on the use of the method in lower organisms. Entitled "Animal Gene Shifted to Bacteria; Aid Seen to Medicine and Farm," the *Times* article described a "practical" method for "transplanting" and amplifying animal genes in bacteria. Although noting the method's scientific value as a means for studying gene expression, McElheny focused on its potential practical uses: "The new method, its discoverers say, gives promise of meeting some of the most fundamental needs of both medicine and agriculture, such as supplies of now scarce hormones, and nitrogen-fixing micro-organisms growing near the roots of wheat and corn plants, thus reducing requirements for fertilizers."[9]

A Stanford University Medical Center news release, timed to appear on the day the paper on the frog DNA was published, also touted the method's likely applications in the

[9] Victor McElheny, "Animal Gene Shifted to Bacteria," *New York Times,* 20 May 1974, p. 1. Three publications, only two of which were written by both Cohen and Boyer, describe the Cohen-Boyer research on gene cloning. The first is Cohen *et al.,* "Construction of Biologically Functional Bacterial Plasmids *In Vitro*" (cit. n. 3); the second, coauthored by Cohen and his laboratory technician, is Annie C. Y. Chang and Stanley N. Cohen, "Genome Construction between Bacterial Species *In Vitro:* Replication and Expression of *Staphylococcus* Plasmid Genes in *Escherichia coli,*" *Proc. Nat. Acad. Sci. USA,* 1974, *71:*1030–1034; the third, which prompted McElheny's article, is John F. Morrow, Cohen, Chang, Herbert W. Boyer, Howard M. Goodman, and Robert B. Helling, "Replication and Transcription of Eukaryotic DNA in *Escherichia coli,*" *ibid.,* pp. 1743–1747.

synthesis of pharmaceuticals and the correction of hereditary defects. It quoted Joshua Lederberg, a recent Nobel laureate and chairman of the Stanford genetics department, who called the method "a major tool in genetic analysis" and suggested that "it may completely change the pharmaceutical industry's approach to making biological elements such as insulin and antibiotics." Although not himself a practitioner, Lederberg had communicated two of the three DNA cloning papers of which Cohen was a coauthor to the U.S. *Proceedings of the National Academy of Sciences* and was well informed about the scientific and commercial possibilities of recombinant DNA technology. The next day the *San Francisco Chronicle* headlined an article "Getting Bacteria to Manufacture Genes" and referred to the possibility of bacteria being transformed into "factories" for the production of drugs such as insulin. (The bacteria-as-factories metaphor was to be endlessly repeated in the years ahead in the commercial promotion of recombinant DNA.) The research also caught the attention of *Newsweek,* which carried an article on the "gene transplanters" and their possible contributions to medicine and agriculture.[10] The message of the procedure's possibly wide commercial utility was hard to miss.

Stanford's Office of Public Affairs routinely sent articles on faculty research of potential commercial interest to Niels Reimers, who directed the university's patenting and licensing effort. (See Figure 1.) Upon receiving the *Times* article, Reimers immediately recognized the discovery as a patenting and licensing opportunity. Reimers was a former engineer who had arrived at Stanford in 1968 with experience in directing contracts at technology-based companies. Noting the university's meagre profits from patents administered by the Research Corporation of New York, in 1969 he had launched a pilot technology licensing program. Faculty members were asked to propose inventions, from which the most commercially promising were to be chosen as the basis for filing patent applications with the United States Patent and Trademark Office in Washington, D.C. To encourage submissions, Stanford structured royalties so that one third was awarded to the inventor, one third to the inventor's department, and one third to university unrestricted funds.[11]

PATENTING AND ENTREPRENEURIALISM IN AMERICAN ACADEMIA

The pilot program with its license marketing focus generated $55,000 in licensing fees in its first partial year, almost ten times more than Stanford had earned in the previous ten years or so. On 1 January 1970 the program was formally established as the Stanford University Office of Technology Licensing, with Reimers as administrator. Its goals were to provide a more efficient mechanism for bringing Stanford's research discoveries forward to public use and benefit and to generate an additional and unrestricted source of income

[10] [News release], Stanford University News Service, 20 May 1974, S74-43, Correspondence 1974–1980, Archives, Office of Technology Licensing, Stanford Univ., Stanford, California (hereafter cited as **OTL Archives**); "Getting Bacteria to Manufacture Genes," *San Francisco Chronicle,* 21 May 1974, p. 6; and "The Gene Transplanters," *Newsweek,* 17 June 1974, p. 54. Lederberg was a scientific advisor to Cetus, a small life science research and development firm founded in the San Francisco Bay Area in 1971. He was thus oriented toward commercialization of discoveries in biomedicine.

[11] Reimers describes his reaction in "Tiger by the Tail" (cit. n. 5). On the pilot licensing program see Niels Reimers, "Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents," an oral history conducted in 1997 by Sally Smith Hughes, Regional Oral History Office, Bancroft Library, Univ. California, Berkeley, 1988 (hereafter cited as **Reimers oral history**), p. 12. Also online: http://www.lib.berkeley.edu/BANC/ROHO/ohonline. On the division of royalties see "Patents" [Stanford patent policy], Oct. 1974, Arthur Kornberg Papers, SC 359, Box 5, Folder: "1980," Green Library, Stanford Univ. For a discussion of patenting and licensing in the university-industry relationship see Roger G. Ditzel, "Patent Rights at the University/Industry Interface," *Society of Research Administrators Journal,* Winter 1983, pp. 13–20.

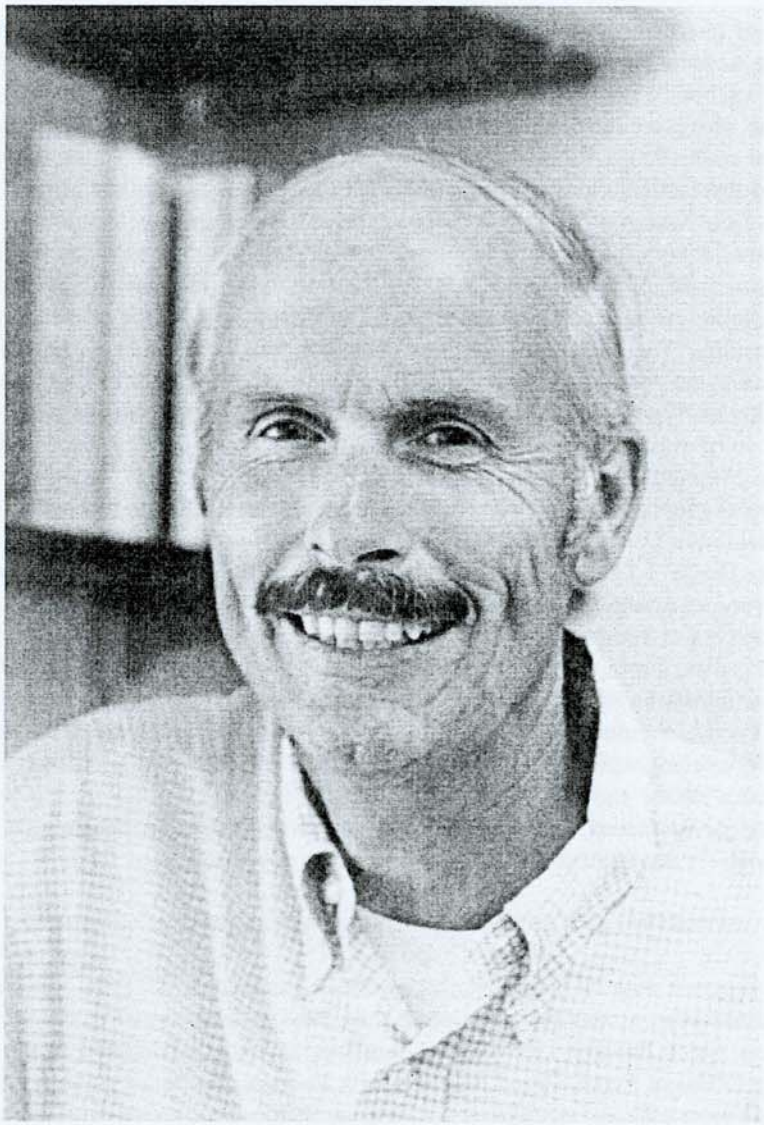

Figure 1. *Niels Reimers, ca. 1980. Photograph courtesy of Office of Technology Licensing, Stanford University.*

to support university education and research. This was a proactive and innovative program of commercialization that few if any other American universities at the time could equal. Most universities of the day lacked the capacity to evaluate, let alone exploit, the commercial potential of faculty research findings.[12]

Stanford's technology licensing program was one aspect of the institution's history of

[12] For the goals of OTL see "Patents"; on Stanford's unusual program see Robert Rosenzweig, seminar on university-industry relationships, 26 Oct. 1999, Center for Studies in Higher Education, Univ. California, Berkeley.

fostering markets for its science. Stanford has long encouraged close interactions with companies in the region, beginning with Frederick Terman's indefatigible promotion of industrial patronage in the 1930s. The university's contribution to the genesis of the electronics industry in Silicon Valley and the creation of the Stanford Research Institute and Stanford Industrial Park are examples of the business orientation of its faculty and administration. If more deliberate, Stanford was far from alone among American research universities in its investment in the world beyond the ivory tower.[13] Beginning early in the twentieth century, many sought patent rights on faculty research discoveries and contracts of one kind or another with government and industry. Stanford, the University of California, Columbia, Wisconsin, and MIT, for instance, have patent policies dating from the 1920s, 1930s, and 1940s and have long held substantial numbers of patents on faculty inventions. Because patenting in academia has a history of controversy, universities have offered a variety of justifications for their engagement in patenting and licensing. Among them are the wish to return patent royalties to research support, to prevent outsiders from profiting at the expense of the university and individual scientists, and to control the uses to which patented inventions are put.[14]

Patenting in academic biomedicine was by tradition especially suspect on ethical grounds, having been explicitly decried in the American Medical Association's Code of Ethics of 1847. Although surgical instruments were freely patented, medical inventions for the relief of the sick were felt to be in a unique ethical category to which those in need should have free and unrestricted access. Harvard, for example, decided in the 1920s to refuse to profit from faculty research in public health and therapeutics and in 1934–1935 formalized the practice in a policy dedicating such patents to the public. In 1975 the institution abandoned this commitment and permitted royalties to be shared among the inventor, the university, and outside entities.[15] Harvard's initial restraint was at one extreme; a number of North American universities from at least the 1910s on did take out patents in biomedicine—but with accompanying publicity that sought to persuade the public that the patent was to its benefit.

Many members of American university faculties, Stanford and UC included, were un-

[13] On Stanford see Rebecca S. Lowen, *Creating the Cold War University: The Transformation of Stanford* (Berkeley: Univ. California Press, 1997); and Stuart W. Leslie, *The Cold War and American Science: The Military-Industrial-Academic Complex at MIT and Stanford* (New York: Columbia Univ. Press, 1993). For an account of American industry's increasing dependence in the twentieth century on university science and engineering see David F. Noble, *America by Design: Science, Technology, and the Rise of Corporate Capitalism* (Oxford: Oxford Univ. Press, 1974), esp. pp. 128–147. For a general treatment of the control of scientific information and the issues it raises see Dorothy Nelkin, *Science as Intellectual Property: Who Controls Scientific Research?* (AAAS Series on Issues in Science and Technology) (New York: MacMillan, 1984).

[14] Richard Shryock, *American Medical Research Past and Present* (New York: Commonwealth Fund, 1947), p. 141. For example, Harry Steenbock at the University of Wisconsin argued that patents on his method for producing vitamin D would allow him and the Wisconsin Alumni Research Foundation, created in 1925 to manage university patents, to protect the public against unscrupulous manufacturers and ensure the quality of commercial products made by licensees: Rima Apple, "Patenting University Research: Harry Steenbock and the Wisconsin Alumni Research Foundation," *Isis,* 1989, *80:*375–394, on p. 376. The University of Toronto made similar arguments regarding its patent on insulin: Michael Bliss, *The Discovery of Insulin* (Chicago: Univ. Chicago Press, 1982), pp. 131–134. On the issues raised by patenting at one university see Henry Etzkowitz, "Knowledge as Property: The Massachusetts Institute of Technology and the Debate over Academic Patent Policy," *Minerva,* Autumn 1994, pp. 283–421.

[15] On medical inventions as a "unique ethical category" see Charles Weiner, "Universities, Professors, and Patents: A Continuing Controversy," *Technology Review,* Feb./Mar. 1986, pp. 33–43; and Shryock, *American Medical Research,* pp. 140–144. On Harvard's policy change see Daniel J. Kevles, "*Diamond v. Chakrabarty* and Beyond: The Political Economy of Patenting Life," in *Private Science,* ed. Thackray (cit. n. 6), pp. 66–79, on p. 67.

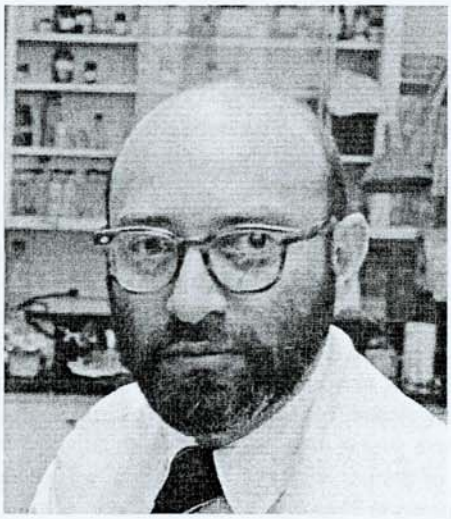

Figure 2. *Stanley N. Cohen, ca. 1975. Photograph courtesy of Office of News and Public Affairs, Stanford University Medical Center.*

comfortable with patenting in academia. Until recently, most professors—except those in scientific disciplines with obvious practical applications, such as engineering, agriculture, and chemistry—were unfamiliar with the requirements of the patent system and gave little consideration to the possibility of commercializing their research discoveries. It was common practice beginning early in this century for activities pertaining to intellectual property to be handled by an outside organization somewhat or entirely distanced from the university, such as the Research Corporation and the Wisconsin Alumni Research Foundation.[16] Thus Stanford in 1970 was an exception among American research universities in having a strong tradition of entrepreneurialism and a dynamic, campus-based technology-transfer operation.

COHEN'S AND BOYER'S REACTION TO PATENTING

Reimers's first step after recognizing the Cohen-Boyer method as a patenting opportunity was to contact Cohen. (See Figure 2.) His suggestion to file a patent application caught Cohen by surprise. As Cohen commented recently, up to this point he had "not . . . dreamed of the notion of patenting any of this." But he had recognized the method's possible practical applications well before the *New York Times* article and spelled out some of them in a paper published earlier in 1974. The opportunity Reimers presented was very different from Cohen's previous experience with patenting. During his postdoctoral years (1965–1967) at Albert Einstein College of Medicine, Cohen had developed a filter box for use in his own research. A salesperson from New Brunswick Scientific had seen him using it and had persuaded Cohen to let New Brunswick patent and market the device. The patent

[16] Reimers oral history, p. 12 (unfamiliarity with patent system); and Martin Kenney, *Biotechnology: The University-Industry Complex* (New Haven, Conn.: Yale Univ. Press, 1986), pp. 74–75 (role of outside organizations). For the role of the Research Corporation as an intermediary between university and industry see Charles Weiner, "Patenting and University Research: Historical Case Studies," *Science, Technology, and Human Values,* 1987, *12*:50–62.

was subsequently assigned to New Brunswick, and Cohen received modest royalties for several years. But the notion of patenting a basic process of laboratory science such as recombinant DNA was new and alien to him. "I suppose," he remarked in an interview, "my framework was that one patents devices, not basic scientific methodologies."[17] As Cohen told Reimers, he was not certain that patenting was appropriate for recombinant DNA, a basic science technique that he felt required many years of development before it reached a point of significant commercial application.[18] Cohen's opinion reflected the academic biologist's unfamiliarity, common at the time, with a prime purpose of the patent system: to spur industry to develop inventions into socially useful products by providing a period of protection.

Cohen's initial resistance to Reimers's suggestion may also have been related to an incongruity between the patenting process and perceptions of science as a communal and cumulative endeavor.[19] Although the patent application procedure requires citation of the research upon which an invention is based, it also aims to reduce the number of inventors to the one or few deemed responsible for the conceptual, rather than merely technical, contribution. Singling out one or a few inventors from a scientific team, as patenting protocol requires, diverged from the custom in scientific publications of assigning individual credit through coauthorship to everyone who had directly contributed to the research being reported. Moreover, compared to scientific convention, the legal definition of inventorship seemed to slight the full dimensions of a scientific discovery, leaving out some collaborators, institutional and personnel resources, and the background of research upon which a discovery is based.[20]

Recalling that he had to talk to Cohen "like a Dutch uncle" in obtaining his permission to file a patent application, Reimers maintained that the commercial development of penicillin had been delayed for eleven years for want of patent protection. This simplification of penicillin history was meant to suggest that a patent would encourage the industrial application of recombinant DNA technology through the sale of license rights. As for Cohen's concern to credit the scientists upon whose research recombinant DNA was based,

[17] Stanley N. Cohen, interview by Sally Smith Hughes, 28 Jan. 1999, draft, pp. 28, 32. (Interviews with Cohen cited in this essay are steps toward an oral history, as yet incomplete.) Having succeeded in splicing and cloning DNA molecules from two different species of bacteria, Chang and Boyer observed: "The replication and expression of genes in *E. coli* that have been derived from a totally unrelated bacterial species . . . now suggest that interspecies genetic transfer may be generally attainable. Thus, it may be practical to introduce into *E. coli* genes specifying metabolic or synthetic functions (e.g. photosynthesis, antibiotic production) indigenous to other biological classes." Chang and Cohen, "Genome Construction between Bacterial Species *In Vitro*" (cit. n. 9). Lederberg communicated the paper in November 1973; it was published in April 1974.

[18] Reimers maintains that Cohen initially believed that commercial development of recombinant DNA might take twenty years: Reimers, "Tiger by the Tail" (cit. n. 5), p. 466. Cohen's recollection is that he projected that the first commercial products would be available in less than ten years: Cohen, personal communication, 19 Jan. 2000.

[19] Jean-Paul Gaudillière and Ilana Löwy point out the transformation in access to knowledge that occurs through patenting: "Patents, and other forms of legal appropriation, mark the symbolic passage from the production of what is viewed as freely circulating knowledge to the production of saleable commodities: thus, they regulate science by guaranteeing legally restricted access to materials, processes, and know-hows." Gaudillière and Löwy, eds., *The Invisible Industrialist: Manufactures and the Production of Scientific Knowledge* (New York: St. Martin's, 1998), "Introduction" to Pt. 3, p. 298.

[20] See Phillippe Ducor, "Coauthorship and Coinventorship," *Science*, 2000, *289*:873, 875. For a discussion and examples of the textual and perceptual distinctions between knowledge claims in science and patent claims in the legal and business sphere see Gregg Myers, "From Discovery to Invention: The Writing and Rewriting of Two Patents," *Social Studies of Science*, 1995, *25*:57–105; for discussion of a patent's creation of a whiggish, internalist version of history see Geof Bowker, "What's in a Patent?" in *Shaping Technology/Building Society: Studies in Sociotechnical Change*, ed. Wiebe E. Bijker and John Law (Cambridge, Mass.: MIT Press, 1992), pp. 53–74.

Reimers responded that "no invention is made in a vacuum"; all are dependent on previous work of other scientists.[21] Patents and the licenses arising from them, he continued, were not only a mechanism for encouraging commercial development of basic science discoveries but also potential generators of unrestricted funds that Stanford could then apply to support university research and education.

Despite his reservations, on 24 June 1974 Cohen completed and signed an invention disclosure on a standard OTL form, the first formal step in the patent application procedure. The one-page disclosure of "A Process for Construction of Biologically Functional Molecular Chimeras" outlined the conceptual genesis of the scientific discovery (Cohen and Boyer's conversation in Hawaii in November 1972), listed the three cloning papers of 1973 and 1974 as the publication base, and noted "many" oral disclosures at seminars and symposia.[22] Only Cohen and Boyer were named as inventors, despite the fact that four other individuals—Annie Chang, Robert Helling, John Morrow, and Howard Goodman—were coauthors of one or more of the papers on which the invention was based. As it turned out, limiting inventorship to Cohen and Boyer would cause problems with Helling and Morrow.

Cohen told Reimers that he would renounce any future royalties to which he was entitled, despite Stanford policy awarding a third to the inventor. He intended the decision to emphasize that his motivation in permitting a patent application to go forward was not the hope of personal gain or aggrandizement but, rather, to provide a possible source of income for the university. The decision was a measure of Cohen's unease concerning the propriety of patenting, but it also turned out to have political advantages. Some years later, after he had been involved in the public debate over regulation of recombinant DNA research, he commented that "the fact that I had already turned over all royalties to Stanford enabled me to speak out in ways which would not have been possible if my motives were being questioned."[23]

Reimers was accustomed to dealing with faculty members of Stanford University Medical School concerning intellectual property matters and in fact had previously worked with Cohen in regard to a copyright on a software-based drug interaction program. At about this time, the medical faculty accounted for approximately 35 percent of OTL's licensed inventions. Thus the stigma historically associated with patenting in medicine does not appear to have deterred some members of the Stanford medical faculty from pursuing patents on their discoveries, perhaps because the inventions were not directly related to patients' health.[24] Nonetheless, there is evidence, to be described later in this essay, of campus dissension about the propriety of patenting in a university environment.

[21] [News release], Stanford University News Service, 3 Aug. 1981, S74-43, Correspondence 1980–1982, OTL Archives ("Dutch uncle"); and Cohen, "Stanford DNA Cloning Patent" (cit. n. 5), p. 215 (Reimers's response).

[22] Stanford University, Invention Disclosure, "A Process for Construction of Biologically Functional Molecular Chimeras"; Inventors: S. N. Cohen, H. W. Boyer; signed and dated: Stanley N. Cohen, 24 June 1974, 74-134-1, Folder: "Cohen, S. et al.," Univ. California Office of Technology Transfer, Oakland (hereafter cited as **UC OTT Archives**). In Greek mythology, a chimera is a creature composed of parts of three different animals. Cohen's use of the term refers to an entity made up of different genetic components.

[23] Niels Reimers to Josephine Opalka, 26 June 1974, 74-134-1, Folder: "Cohen, S. et al.," UC OTT Archives (renouncing royalties); and Nicholas Wade, "Cloning Gold Rush Turns Basic Biology into Big Business," *Science,* 1980, *208:*688–692, on p. 689. At a later date, Cohen reversed his decision and began to take his share of the licensing income so that he had some control over its use: Cohen, personal communication, 10 July 2000.

[24] Reimers oral history, p. 3 (earlier work with Cohen); and Debby Fife, "The Marketing of Genius," *Stanford Magazine,* n.d., [1975 or 1976], pp. 48–53 (35 percent). Of the six medical patents generating royalties for Stanford in 1977, the most lucrative was an instrument, the fluorescence-activated cell sorter produced by Becton Dickinson Electronics. See Bill Snyder, "Discoveries: Finding the Way to the Marketplace," *Stanford MD,* Spring 1977, pp. 18–23.

Shortly after his conversation with Reimers, Cohen had telephoned Boyer to broach the possibility of filing a patent application. Up to this point, Boyer had not considered trying to patent the cloning procedure. He commented recently: "It was certainly not Stanley's idea or my idea to [patent] it. Very few molecular biologists [at the time] knew anything about patents, their place in science and business, and even in the vitality of our country." Nonetheless, Boyer had already considered possible commercial applications of recombinant DNA. The work with frog DNA indicating that genetic material from a higher organism could be cloned in bacteria had suggested the intriguing possibility of using the method to clone human genes in bacteria and express them as human proteins: "we were thinking about [commercial applications] at that time [of the frog experiments, 1974]. Not in any grandiose ways, but sitting around the laboratory talking about, Well, now if you can clone eukaryotic [higher organism] DNA, you can clone the gene for human insulin or human growth hormone or whatever you can think of, and you should be able to make it in a bacterium."[25]

Boyer reacted to Cohen's call by questioning whether Stanford and UC had the right to patent research that had been partially funded by the National Institutes of Health (NIH); only the federal government, he mistakenly believed, could hold title to a patent arising from research it had supported. Cohen then explained to Boyer what Reimers had explained to him: their method was potentially patentable under Stanford's institutional patent agreement (IPA) with NIH. Like many other American research universities, Stanford had negotiated an IPA with the Department of Health, Education, and Welfare (DHEW). Until passage of the Bayh-Dole Act of 1980 simplified patent policy regarding federally funded research, a university wishing to patent the results of work supported by a federal agency was required to petition DHEW for transfer of ownership of each invention it sought to patent to the university.[26] This cumbersome procedure accomplished, the university could then seek patent protection and hold title if the patent issued.

Satisfied with Cohen's clarification concerning Stanford's IPA and attracted by the commercial possibilities of recombinant DNA, Boyer had no further hesitation in proceeding with a patent application. He was unwilling, however, to renounce his personal share of any future royalties, despite Cohen's decision to do so. Of the two inventors, Boyer was to be less involved in the patenting and licensing processes, in part because Stanford, with UC consent, took the lead in all aspects of patent prosecution. Unlike Cohen, Boyer was quite willing to let others handle the patenting process, stepping in only when his input was critical: "I must admit, I didn't have a lot of patience with patent law and trying to figure it out. So I just told [Bertram Rowland, the patent attorney] everything I knew, and the guy went ahead and did it [i.e., filed a patent application]. Stanley helped him out quite a bit; they were always working on it together. I tossed in a few ideas."[27]

The readiness with which Boyer accepted Stanford's proposal to file a patent application may have reflected his institutional environment. While UCSF in the 1970s did not have

[25] Boyer interview by Hughes, 22 July 1994, 28 Mar. 1994, draft, pp. 168, 60.

[26] Boyer interview by Hughes, 27 July 1994, draft, p. 170. For a description of DHEW procedure for patenting prior to and after Bayh-Dole see Nelkin, *Science as Intellectual Property* (cit. n. 13), pp. 13–15. Nelkin states that of some thirty thousand government-owned patents, only 4 percent had been marketed as of 1979.

[27] Boyer interview by Hughes, 27 July 1974, draft, pp. 167–169, on pp. 168–169; and William Carpenter to Reimers, 18 Sept. 1974, S74-43, Correspondence 1974–1979, OTL Archives (on Boyer's unwillingness to renounce royalties). Cohen agrees that Boyer was not eager "to spend the time" on patenting and that "most of the details of the patents . . . were left to me": Cohen interview by Hughes, 28 Jan. 1999, draft, pp. 39–40.

a strong history of commercial interests and ties with industry, it was a health sciences campus in which basic research and clinical application were occurring side by side. The School of Medicine, in which Boyer was an associate professor of microbiology working in the arcane field of bacterial restriction enzymes, was at this time strengthening its basic science enterprise by hiring young faculty skilled in the latest molecular techniques. It was a culture focused on the synergism of basic biomedical science and clinical medicine in which practical application was a clear goal, even though patenting played only a minor role. Intent on extending the basic science of recombinant DNA—and also engaged in Vietnam War protests and other liberal causes—Boyer regarded the patent application as a peripheral matter, one that Stanford and Stanley Cohen seemed well capable of handling. This viewpoint was in keeping with the "laid-back" image he projected, with his cap of brown curls and jeans-and-running-shoes style of dress—"a baroque angel in blue jeans," as the *Wall Street Journal* later described him.[28]

In contrast, Cohen was and is a more cautious and reticent personality. He immediately saw and was preoccupied by the ethical dilemmas that patenting presented. His concern that a patent did not acknowledge the body of research on which any invention is built was perhaps related to his own care to ensure that he and his laboratory received proper scientific credit.[29] At one point Cohen had considered becoming a rabbi but instead had gone to the University of Pennsylvania Medical School; he subsequently decided to combine a career in clinical medicine with basic biological research. He arrived at Stanford in 1968 with an appointment as an assistant professor in the Department of Medicine. In the early 1970s he was balancing clinical responsibilities and commitment to his molecularly based research on bacterial plasmids—circles of DNA independent of the nucleus—as bearers of antibiotic resistance, a basic science problem with obvious clinical relevance.

THE UNIVERSITY OF CALIFORNIA: A SECONDARY PARTNER

On 26 June 1974 Reimers sent Cohen's invention disclosure to Josephine Opalka, an administrator at the University of California patent office in Berkeley that handled patenting and licensing activities for the sprawling University of California system. Reimers had first contacted Opalka on 20 May, the day the *New York Times* article appeared, to alert her to the possibility of a patentable invention for Stanford and UC. Since the cloning method was a joint discovery by professors at the two institutions, both universities would have to agree to proceed with a patent application. Opalka reported that UC supported an application and was amenable to having Stanford administer the invention under its IPA with NIH. But she objected to Reimers's proposal that UC share the expense of filing the

[28] Quoted in William Boly, "The Gene Merchants," *California Magazine,* 1982, 7:76–79, 170–172, 174–176, 179, on p. 170. Restriction enzymes, made by bacteria, "restrict" or cut DNA molecules at specific nucleotide sequences; they are an important component of the recombinant DNA process. In 1975 Boyer and his laboratory left the Department of Microbiology to join the Department of Biochemistry, where he was given space in newly opened laboratory towers. For an account of the rise of molecular biology at UCSF see William J. Rutter, "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco," an oral history conducted in 1992–1993 by Sally Smith Hughes, Regional Oral History Office, Bancroft Library, Univ. California, Berkeley, 1998. Also online: http://www.lib.berkeley.edu/BANC/ROHO/ohonline.

[29] Both Cohen and Boyer speak in the interviews toward the preparation of their oral histories of the debate over the order in which the authors should be listed on the 1973 and 1974 papers: Cohen interview by Hughes, 1 Mar. 1995, draft, p. 28; and Boyer interview by Hughes, 22 July 1994, draft, pp. 153–155.

patent application. Not wanting to relinquish a chance for commercialization, Reimers agreed to proceed at Stanford's expense. Opalka, who understood the scheme to involve no initial cost or risk to UC, decided that there was thus no need to solicit the customary opinions as to the invention's commercial viability from scientists in the field.[30]

The UC patent office, according to Reimers, was in the mid 1970s "overloaded with technology that they didn't move. They did not market [licenses]; they'd wait for a company to come to them, instead of taking the very proactive way we did it at Stanford. So this invention of Cohen and Boyer was just one more thing to do." Although Reimers can hardly be considered an unbiased observer, some members of the UC faculty today agree that in the 1970s the university's patenting and licensing activities did not adequately capitalize on the inventiveness of its faculty. The university owned a number of royalty-producing patents but did not invest sufficient financial or personnel resources to make licensing a priority until the early 1980s. As late as 1977 the UC Board of Patents, which oversaw activities of the university patent office, though aware of the commercial potential of UC discoveries in genetic engineering, recommended a low-key approach to the commercialization of university inventions: "Inventions and patents should continue to be considered as fortuitous by-products of research, nothing more." Many on the Berkeley faculty, known for its liberal cast, felt that the university should not be in "the invention business."[31] In short, until the last two decades of the century, the focus of UC patent policy was on making faculty inventions available to the private sector; marketing and making money from them were secondary concerns. It was a far cry from the situation at Stanford.

In August 1974 Reimers wrote to NIH to set the IPA approval process in motion. Noting "the tremendous significance of this invention," he doubtless expected patent prosecution to proceed more or less routinely.[32] Such was not to be the case.

THE RECOMBINANT DNA CONTROVERSY: A COMPLICATION IN THE PATENTING EFFORT

The politically fraught context of biology in the mid 1970s was to be a formidable factor in the effort to patent the Cohen-Boyer procedure, influencing how Stanford and UCSF conducted and publicly presented the patenting process and raising the question of whether a patent should be sought at all. The event precipitating concerns about the safety and implications of recombinant DNA research had occurred five months before the first Cohen-Boyer paper appeared in print. Despite his agreement with Cohen to keep the discovery quiet until after publication, an ebullient Boyer had revealed to some 130 scientists attending the Gordon Conference on Nucleic Acids in June 1973 that he and his colleagues

[30] Reimers to Opalka, 2 May 1975, 74-134-1, Folder: "Cohen-Boyer Exploitation," UC OTT Archives; Opalka to Reimers, 19 Aug. 1974, 74-134-1, Folder: "Cohen, S. et al.," UC OTT Archives; Reimers, personal communication, 22 Dec. 1999 (Opalka's unwillingness to share filing expense); Opalka to Dr. Robert N. Hamburger, 14 May 1975, 74-134-1, Folder: "Cohen, S. et al.," UC OTT Archives (Reimers to proceed at Stanford's expense); and Josephine Opalka, telephone interview by Sally Smith Hughes, 3 June 1999. Both university patent offices routinely relied on evaluations from scientists in the field to help them decide whether to proceed with the expensive patenting process.

[31] Reimers oral history, p. 4; for corroboration of Reimers's view from a UC faculty member see William J. Rutter, interview by Sally Smith Hughes, 31 May 1999, draft, pp. 1–2, 10–12, passim. On the policy in 1977 see John A. Perkins to UC President David Saxon, 4 Apr. 1977, CU-6, UC (System), Office of Technology Transfer, Box 61, Folder: "Board of Patents, Priority Administration, file #1, 7/24/57–12/31/76," Bancroft Library Univ. California, Berkeley. The laissez-faire policy was to change in the early 1980s, when for the first time experts trained in patent law and licensing were hired to staff UC's technology transfer office. The phrase "the invention business" was used by a participant who prefers anonymity.

[32] Reimers to Norman J. Latker, 20 Aug. 1974, S74-43, Correspondence 1974–1979, OTL Archives.

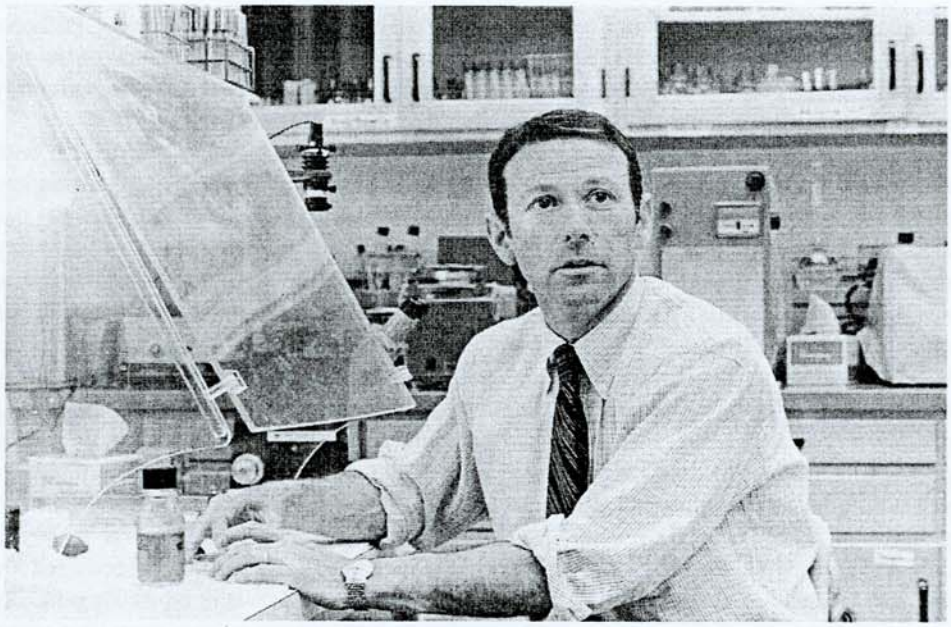

Figure 3. *Paul Berg, 1972. Photograph courtesy of Office of News and Public Affairs, Stanford University Medical Center.*

had developed a method for splicing and cloning DNA. A participant's comment—"Well, now we can put together any DNA that we want to"—brought home the significance and to some the potential danger of the new technical capability.[33]

To summarize history that has been told in detail elsewhere, conference participants were concerned that genetically engineered molecules might prove hazardous for laboratory workers and the public. They voted to have Maxine Singer and Dieter Soll, cochairs of the Gordon Conference, write letters to the National Academy of Science (NAS) and the Institute of Medicine requesting the formation of a committee to investigate the potential risk of recombinant DNA research and the possible need for research guidelines. The academy subsequently formed the Committee on Recombinant DNA to study the problem, with the Stanford biochemist Paul Berg at its head. (See Figure 3.) In July 1974, while the patenting issue was being considered at Stanford, the committee published a letter in *Science* calling for a voluntary moratorium on certain kinds of recombinant DNA research until a conference could be convened to assess risks and develop research guidelines.[34] Berg's name was first on the list of ten scientists who signed the letter; Cohen and Boyer were also signatories.

Stanford and UCSF were at the time at the forefront of the science of recombinant DNA.

[33] John Lear, *Recombinant DNA: The Untold Story* (New York: Crown, 1978), p. 70.

[34] For commentary on and reproductions of key documents associated with the controversy over and the commercialization of recombinant DNA see James D. Watson and John Tooze, *The DNA Story: A Documentary History of Gene Cloning* (San Francisco: Freeman, 1981). The Singer-Soll letters are reproduced on pp. 5 and 6; the letter published in *Science* is reproduced on p. 11. For a detailed history see, e.g., Krimsky, *Genetic Alchemy* (cit. n. 8), pp. 70–96.

Because Cohen's plasmid was at first the only vector suitable for use in recombinant DNA research, he received requests for it from other scientists even before the November 1973 paper had appeared. Although initially insistent on refusing such requests until the paper was published, about six weeks before publication Cohen gave in to the pressure and began to send the plasmid to scientists if they agreed to follow safety precautions of his own construction. For their part, Boyer and his laboratory were further developing restriction enzyme technology and exploring the potential of DNA cloning as a general procedure in molecular genetics.[35] But the politics of the recombinant DNA debate could not be divorced from the science, and it was the Stanford campus that was its political center. Berg, as head of the NAS committee, was arguably the most visible figure in the controversy and a forceful spokesman for the need to assess risks and devise research guidelines. Among his many other activities in 1974, including the chairmanship of the Stanford biochemistry department, he began to organize an international conference, the now-famous Asilomar Conference on Recombinant DNA Molecules, which would convene on California's Monterey Peninsula in February 1975. Its purpose was to review progress in recombinant DNA research and to discuss biosafety guidelines so that the voluntary moratorium on recombinant DNA experiments could be lifted.[36]

The high-profile conjunction of recombinant DNA research and politics on the Stanford campus presented a major problem for those interested in commercializing the Cohen-Boyer discovery. Stanford and UC documents concerning patenting of the procedure begin in the summer of 1974 to reflect a pervasive theme of the next few years: how to accommodate the patenting and licensing effort and the biohazards controversy. Could the process of commercialization be prevented from exacerbating the political problem? Reimers assured NIH that Stanford intended "to exercise great care in the administration of this invention, insofar as is feasible within the constraints of the patent grant which may be issued, to ensure against misuse of the invention." He believed, however, that the appropriate mechanism for controlling recombinant DNA research was not the power of the patent holder but, rather, "the restraint that individuals of the international scientific community must exercise against uncontrolled [recombinant DNA] experimentation."[37] In so saying, he was departing from the traditional argument of American universities that owning a patent enabled a university to monitor use of the invention it protected.

[35] Lear, *Recombinant DNA* (cit. n. 33), pp. 83–84 (sharing the plasmid); and Howard M. Goodman, Herbert W. Boyer, Department of Biochemistry and Biophysics, UCSF, Annual Report 1974, Library, UCSF Department of Biochemistry, [n.p.]. Goodman and Boyer had agreed at this time to collaborate in research and include each other's names as authors of publications. The arrangement soon disintegrated.

[36] Paul Berg, David Baltimore, Sydney Brenner, Richard O. Roblin III, and Maxine Singer, "Asilomar Conference on Recombinant DNA Molecules," *Science,* 1975, *188*:991–994. Robert Bud points out that, rather than marking the beginning of concerns about genetic engineering, Asilomar represented the culmination of almost two decades of such concerns: Bud, *Uses of Life* (cit. n. 1), p. 175. Berg was chairman from 1969 to 1974, having followed Arthur Kornberg to Stanford in 1959 when the latter became the first chairman of the new biochemistry department. Both Kornberg and Berg, longtime colleagues and friends, recount in their oral histories the story of how almost the entire Kornberg laboratory migrated from Washington University, St. Louis, to Stanford: Arthur Kornberg, "Biochemistry at Stanford and Biotechnology at DNAX," an oral history conducted in 1998 by Sally Smith Hughes, Regional Oral History Office, Bancroft Library, Univ. California, Berkeley, 1998; and Paul Berg, "A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry," an oral history conducted in 1998 by Sally Smith Hughes, Regional Oral History Office, Bancroft Library, Univ. California, Berkeley, 2000. The Kornberg oral history is online: http://www.lib.berkeley.edu/BANC/ROHO/ohonline.

[37] Reimers to Latker, 20 Aug. 1974, S74-43, Correspondence 1974–1979, OTL Archives.

ASSESSING THE COMMERCIAL POTENTIAL OF RECOMBINANT DNA

The political controversy was only one of Reimers's problems. He also had the patent bar to consider. U.S. patent law requires a patent application to be filed within the year following the first public disclosure of the invention. The first paper on the cloning method had been published in November 1973; Reimers was all too aware that the deadline of November 1974 was fast approaching. He had not heard about the work until May 1974 and was now hard pressed to make a final decision as to whether a patent application was in Stanford's best interest and, if so, to file an application before the bar. Yet it was not known whether industrial application of recombinant DNA technology was practical. Facing an uncertain market, Reimers assigned William Carpenter, one of the Stanford business school master's degree candidates whom he habitually hired for summer work at OTL, to investigate its commercial potential. This was routine practice: Reimers would proceed with the costly patenting procedure only if corporations expressed interest in developing the invention and the university had a reasonable chance of recouping the financial outlay through licensing fees and royalties.

Carpenter's first step was to schedule separate meetings with Cohen and Boyer for the purpose of exploring possible practical uses of the cloning method. Although no record has been found of his meeting with Cohen, there are handwritten notes of his discussion with Boyer. Elated about the method's expanding use in basic research, Boyer also saw immediate commercial applications in the synthesis of certain hormones and enzymes. He predicted that the new procedure, by increasing the yield of these substances from bacterial sources, would be of interest to commercial concerns in microbiology and suggested that it could also be used to produce antigens for the synthesis of antibodies. Boyer mentioned insulin, a drug with a highly profitable worldwide market, as another target but cautioned that there was "much work to be done before such applications can be made."[38] Thus, more than eighteen months before he cofounded the biotechnology company Genentech in April 1976, Boyer had definite ideas about specific commercial uses of recombinant DNA technology.

Carpenter's report to Reimers, based on his discussions with Cohen and Boyer, described the "plasmid gene transplantation technique" as a means of turning bacteria into "genetic factories" for the production of "hard-to-make" substances such as insulin, viral proteins for vaccine synthesis, hormones, and other proteins. The assessment provided the justification Reimers sought for proceeding with a patent application. But he had to move quickly if the university was to meet the patent bar, now only a few weeks away. As it was, Stanford and UC had lost the chance to obtain foreign intellectual property rights on recombinant DNA; the "first-to-file" patent system operating abroad precluded filing a patent claim on a previously published invention. Reimers engaged Bertram Rowland, a patent attorney whose San Francisco law firm had an office in Palo Alto, to work with Cohen and Boyer to draw up a patent application. On 4 November, just one week before the bar, Stanford in coordination with the University of California filed a patent application entitled "Process and Composition for Biologically Functional Molecular Chimeras."[39] As

[38] Carpenter to Cohen, 4 Sept. 1974; and BC [Bill Carpenter] to File S74-43, re: Dr. Herbert Boyer, 18 Sept. 1974: S74-43, Correspondence 1974–1979, OTL Archives.

[39] Carpenter to Reimers, 18 Oct. 1974, S74-43, Correspondence 1974–1979, OTL Archives; and "Cohen-Boyer Application," Serial No. 520, 691, filed 4 Nov. 1974, CU-6, UC (System), Office of Technology Transfer, Box 52, Exhibit Book II, Bancroft Library, Univ. California, Berkeley. Many countries require a patent application to be filed before the invention is published. One estimate is that Stanford and UC lost 50 percent of

the title states, the application was for a patent on both the recombinant DNA process and product (or "composition," in patenting jargon).

In August 1975 OTL again approached Boyer about commercial development of the recombinant DNA process. Practical applications had to be demonstrated, Boyer pointed out, before the pharmaceutical industry could be expected to make any significant capital investment in developing the technology. To provide just such a demonstration, Boyer planned to establish "a general synthesis procedure for small polypeptide hormones."[40] He proposed to make the hormones by synthesizing DNA, using chemicals off the shelf rather than employing the natural genes. Using recombinant DNA technology, the artificial gene would then be cloned in bacteria. One considerable advantage of the synthetic DNA approach was that it would not be subject to the NIH guidelines. Then being formulated in the wake of the Asilomar conference, these guidelines were to set forth physical and biological containment standards designed to reduce the chance of biohazard arising from recombinant DNA research involving living organisms and natural genes; synthetic genes made in a test tube, as Boyer envisioned, would not fall under their purview.

Because of their limited supply, Boyer believed the production of human hormones to be the most immediately promising field for commercial development of recombinant DNA technology. His proposed target was angiotensin-2, a hormone that causes vasoconstriction, which Boyer chose for its small size and resulting ease of synthesis. He told OTL that he expected the synthesis to be completed by unnamed "collaborative German biochemists" on 1 September 1975. "Once the [synthetic DNA] sample is received," the OTL memo continued, "approximately three months of basic test work will be required to determine whether synthesis of the hormone can be achieved by the recombinant DNA process. If this procedure is successful, the next logical extension would focus on the production of insulin."[41]

Thus angiotensin was merely the first step in Boyer's scheme to establish the commercial viability of the recombinant DNA process in the production of drugs for human use. He chose insulin as a target because it was a product with far greater medical significance and commercial value than angiotensin. Human insulin, he projected, should have none of the adverse side effects sometimes occasioned by use of the bovine and porcine insulin currently on the market. Its relatively small size for a biological molecule also held promise that the synthetic process might be less laborious than that for some larger molecules. Commercial development could proceed more quickly, Boyer commented, if he had the help of "organic chemists" in synthesizing DNA molecules. He asked OTL to contact firms to determine their interest in supporting development work of this nature. Boyer's ideas had advanced a step: by the summer of 1975 he not only had aspirations for commercial development of recombinant DNA and DNA synthesis but had also devised a research approach and selected drug targets.[42]

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potential licensing revenue from the Cohen-Boyer discovery because of the lack of foreign patent rights: Kenneth S. Dueker, "Biobusiness on Campus: Commercialization of University-Developed Biomedical Technologies," *Food and Drug Law Journal,* 1997, *52:*453–509, on p. 493 n 256.

[40] Ken Imatani to Reimers, memo, "Discussion with Dr. Boyer for Future Development Work for Recombinant DNA Process," 6 Aug. 1975, S74-43, Correspondence 1974–1979, OTL Archives.

[41] *Ibid.*

[42] *Ibid.* In a May 1975 interview Boyer mentioned his current work on the expression of genes of higher organisms in bacteria and went on to remark: "I think this has a lot of implications for utilizing the technology in a commercial sense, that is, could one get bacteria to make hormones, etc., etc." Herbert Boyer, interview by Rae Goodell, 20 May 1975, Recombinant DNA Controversy Oral History Collection, Institute Archives and Special Collections, MIT Libraries, Cambridge, Massachusetts, p. 35.

No evidence has been found that research by "German biochemists" ever transpired. Instead, Boyer began to contemplate forming a commercial venture of his own. In January 1976 he was visited by the venture capitalist Robert Swanson, who was likewise interested in creating a company based on the recombinant method. Their discussions led to the formation of Genentech, Inc.—*Gen*etic *En*gineering *Tech*nology—in April 1976. Boyer and his UCSF laboratory group immediately began collaborating in work financed by Genentech on the synthesis of somatostatin, another small-molecule hormone and the company's first research project. He and Swanson held the work to be a critical test both of recombinant DNA technology as a new commercial approach to drug synthesis and of the future viability of Genentech, the first company founded to exploit that technology.[43]

The discovery that industrial research was being conducted and funded in a public institution divided the UCSF Department of Biochemistry and prompted a campus investigation. The personal hostility directed at Boyer left enduring scars and suggested the novelty and precarious state of corporate relationships in academic biology at the time. He was an early target of the tensions that were to erupt throughout academia in coming years as universities and scientists at the forefront of molecular biology sought to capitalize on commercial opportunities.[44]

DISSENSION REGARDING THE PATENT APPLICATION

In January 1975, after confirming that the fundamental concept for the recombinant DNA discovery originated with Cohen and Boyer alone, Rowland wrote to the four coauthors of the 1973 and 1974 papers on which the patent application was based, asking them to disclaim inventorship. This was a precaution, not a requirement of patent law, which Rowland hoped would deter the U.S. Patent Office examiner from questioning Cohen's and Boyer's status as sole inventors. Rumors circulated that Helling and Morrow refused to sign the affidavits. Cohen was distressed that Rowland had not consulted him before sending the letter and by his colleagues' reaction to it. The incident served to heighten his lingering discomfort with Stanford's patenting effort, particularly in light of mounting tensions associated with the recombinant DNA controversy. He wrote Rowland that the

[43] On the work financed by Genentech see Herbert Boyer, Associate Professor of Biochemistry, Department of Biochemistry and Biophysics, University of California, San Francisco, Annual Report 1975, published May 1976, Library, UCSF Department of Biochemistry; and "Sponsored Research Agreement between Genentech, Inc., and the Regents of the University of California," 1 Aug. 1976, 77-064-1, Folder: "Goodman et al., Rutter et al., Deposit of Microorganisms," UC OTT Archives. For publicity on the somatostatin project see "Synthetic DNA Put to Work in Living Cells" [press release], UCSF News Services, 28 Oct. [1977]; and "A Commercial Debut for DNA Technology," *Business Week,* 12 Dec. 1977, pp. 128–129.

[44] On the campus investigation see James E. Cleaver, Chairman UCSF Biosafety Committee, to Chancellor Francis A. Sooy, 4 Nov. 1977, Sooy to Cleaver, 9 Nov. 1977, AR86-7, Carton 2, Folder 76, Archives and Special Collections, UCSF Library; and "UC Funds Aid Private Groups," *Los Angeles Times,* 7 Sept. 1978, p. 1. On the hostility directed at Boyer see Boyer interview by Hughes, 30 Apr. 1994, draft, pp. 139–143. In a newspaper article triggered by Genentech's successful production of somatostatin, Boyer gave a simple explanation for his participation in the company: "I wanted to see that the technology gets transferred to private industry so that the public benefits come out as soon as possible." Charles Petit, "The Bold Entrepreneurs of Gene Engineering," *San Francisco Chronicle,* 2 Dec. 1977, p. 2. The science media of the late 1970s and 1980s is rife with articles on the promise and problems of greater university-industry interaction in biomedicine. See, e.g., the response of the president of Harvard to the public furor when the university contemplated investing in a company formed by a Harvard professor to commercialize DNA research: [Derek C. Bok], "Business and the Academy," *Harvard Magazine,* May–June 1981, pp. 23–35. The controversy over the proper boundary between academic and industrial research continues. See, e.g., the reaction to UC Berkeley's alliance in 1998 with Novartis Agribusiness Discovery Institute: "UC Finalizes Research Deal with Biotech Firm; Pie Tossers Leave Taste of Protest," *San Francisco Chronicle,* 24 Nov. 1998, p. A17.

letter had given recipients the impression that he and Boyer were personally filing the patent application and sought to profit financially if a patent was issued. He was anxious to clarify for his colleagues that it was Stanford as an institution, rather than he and Boyer as individuals, that chose to pursue a patent application. He then stated his reason for succumbing to Reimers's request to file a patent application: "I can accept the view that it is more reasonable for any financial benefits derived from this kind of scientific research carried out at a non-profit university with public funds to go to the university, rather than be treated as a wind-fall profit to be enjoyed by profit-motivated businesses; I agreed to cooperate with Stanford for that reason."[45]

In an effort to quell any discussion that he was pursuing a patent for personal financial gain, Boyer at this point reversed his position and announced that he would not accept royalties from any future patent.[46] His decision indicated the sensitivity of this particular situation but was reinforced by the ambivalent position patenting occupied in academia at this time, even at a university as entrepreneurial as Stanford.

In early February 1975, less than three weeks before the Conference on Recombinant DNA Molecules was to convene at Asilomar, Cohen and his Stanford colleagues David Hogness, Charles Yanofsky, Ronald Davis, and Paul Berg, who were using recombinant DNA in research on a variety of organisms, met with Reimers in Berg's office in the biochemistry department of the medical school. Berg—and perhaps Hogness, Yanofsky, and Davis as well—had only recently learned of the patent application. The meeting had been called to discuss whether the scientists due to assemble at Asilomar might accuse Stanford of conflict of interest. It was common knowledge in molecular biology that Berg was spearheading the assessment of the risks and benefits of recombinant DNA research.[47] Yet his own university was simultaneously seeking patent ownership of the technology for the purpose of encouraging industrial development.

Those gathered in Berg's office were exquisitely aware that there could be adverse political fallout from Stanford's patenting effort. A false step ran the danger of igniting the biohazards controversy, tarnishing the public image of the two universities, and adversely affecting the future course of recombinant DNA science and its commercial application. The meeting was strained. Berg was opposed to any endeavor that would dilute his influence as a spokesman for creating federal regulatory policy so that the moratorium could be lifted, research guidelines formulated, and the application of recombinant DNA in basic research fully exploited. He was also concerned about the breadth of the Cohen-Boyer patent application, which claimed title to "production of all possible recombinants, joined in all possible ways, cloned in all possible organisms, using all possible vectors." In his view, the method Cohen and Boyer had devised was a basic building block of genetic engineering that should not be privatized. As he explained three years later: "I had certainly not been in support of the patent application. I thought it was the wrong time, the wrong kind of effort that the university should be making."[48]

[45] Reimers, personal communication, 22 Dec. 1999; and Cohen to Bertram I. Rowland, 22 Jan. 1975, S74-43, Correspondence 1974–1979, OTL Archives.

[46] Reimers to William Massy, 10 Feb. 1975, S74-43, Correspondence 1974–1979, OTL Archives. Boyer later donated his share of net royalties to a fund in the UCSF Department of Biochemistry that is currently known as the Herbert W. Boyer Fund.

[47] On the meeting see Reimers to Massy, 10 Feb. 1975. Although associated in the public mind with the speculative risks of recombinant DNA technology, Berg was not only aware of but also, as early as 1974, a spokesman for the projected benefits of the technology in producing antibiotics, hormones, and food sources: Bud, *Uses of Life* (cit. n. 1), p. 178.

[48] Paul Berg, interview by Charles Weiner, 17 Apr. 1978, Recombinant DNA Controversy Oral History Col-

Cohen's response reflected his informal tutorials with Reimers on the patenting process: broad patent claims and narrow determination of inventorship were common objectives of the patent system, however inimical they might seem to traditional scientific values. The group meeting in Berg's office debated whether Stanford should proceed as planned with patent prosecution, turn the invention over to the Research Corporation for patenting, or abandon the patent application entirely—without resolution.[49]

What is not reflected in surviving documentation of this and other encounters between Cohen and Berg is the undercurrent of personal animosity. In 1972, a year before the first Cohen-Boyer publication, Berg and colleagues had published their method for joining DNA segments and transferring the recombinant molecules to bacteria. It was a sophisticated procedure requiring special enzymes and expertise that only the Stanford biochemistry department at the time could provide. Since his arrival at Stanford Cohen had been given access to the biochemistry department's resources, intellectual and material, that were not available in his own Department of Medicine. Now he and Boyer, outside the inner core of Stanford biochemistry, had developed a technique so simple that virtually any molecular biologist could master it.[50] Although Cohen repeatedly acknowledged the groundwork scientists at Stanford and elsewhere had provided, Berg felt that his own role and that of others in the development of recombinant DNA had been slighted. The patent application, with only Cohen and Boyer listed as inventors, added a personal grievance to Berg's political objections.[51]

Joshua Lederberg was another opponent of patenting the Cohen-Boyer work, even though he appreciated and even expounded its commercial promise. He saw patenting in academia as a barrier to open scientific communication. Arthur Kornberg had similar reservations. The opposition of Lederberg, Kornberg, and Berg—the first two Nobel laureates, the third a leading scientist in the media limelight, and all three former or current Stanford department chairmen—was another problem to be negotiated by those interested in patenting the Cohen-Boyer procedure.[52] Although these three were not the only academics to find problems with the Stanford-UC patenting effort, their power and prestige and the fact that they were able to meet face to face with those pursuing patent prosecution made it all but impossible for Stanford to ignore their viewpoint. This was one of many situations occurring throughout the patenting process in which Stanford was compelled to

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lection (cit. n. 42), pp. 71, 70 (quotations); and Reimers to Distribution [Cohen, Daniel Federman, Robert Lehman, Clayton Rich, Robert Rosenzweig], 15 Nov. 1976, S74-43, Correspondence 1974–1979, OTL Archives.

[49] John Poitras to File S74-43, 21 May 1976, S74-43, Correspondence 1974–1979, OTL Archives.

[50] David Jackson, Robert Symons, and Paul Berg, "Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40," *Proc. Nat. Acad. Sci. USA,* 1972, *69:*2904–2909. The complex history, much simplified here, of the simultaneous development at Stanford of various approaches to recombining DNA is told in detail in the Berg oral history (cit. n. 36). Only the Cohen-Boyer method enabled cloning of the recombinant DNA.

[51] Reimers remarked recently: "I was *so* glad when [Berg] got that [Nobel Prize]. . . . I was feeling bad before then, because Paul was a distinguished scientist, and he had been very upset with the patenting process and not being recognized." Reimers oral history, p. 38. For an example of Cohen's acknowledgment of earlier work see Stanley N. Cohen, "The Transplantation and Manipulation of Genes in Microorganisms," in *The Harvey Lectures* (Series 74) (New York: Academic, 1979), pp. 173–204.

[52] For Lederberg's position see Joshua Lederberg, "DNA Research: Uncertain Peril and Certain Promise," *Prism,* Nov. 1975, *3:*33 (rpt. in Watson and Tooze, *DNA Story* [cit. n. 34], pp. 56–60); for Kornberg's views on patenting see Arthur Kornberg, *The Golden Helix: Inside Biotech Ventures* (Sausalito, Calif.: University Science Books, 1995), pp. 231–254. The Nobel Prize that Berg would share in 1980 for "his fundamental studies of the biochemistry of nucleic acids with particular regard to recombinant DNA" is one measure of his standing in science. See Gina Bari Kolata, "The Nobel Prize in Chemistry," *Science,* 1980, *210:*887–889. Lederberg was chairman of genetics and in 1969 Berg followed Kornberg as chairman of biochemistry.

weigh the benefits of commercialization against its political liabilities and to adjust activities in light of faculty dissension and broader social and political developments.

On 7 April 1975, more than a month after the Asilomar conference had concluded, the same group, with the addition of a Stanford provost, met for a second time. Reimers reported that tensions within the group regarding the Cohen-Boyer patent application had "defused" since the previous meeting; no one at the Asilomar conference had made an allusion to it. The presence of the provost suggests that top Stanford administrators were by this time aware that the intersection of the patent question and the recombinant DNA debate could be politically explosive and required high-level administrative oversight. They were also beginning to appreciate that the patent, if granted, might become the impressive royalty generator that the university had thus far never had. Berg and Yanofsky were sufficiently concerned about the propriety of the patenting effort that they had consulted officials at two federal science agencies. Reimers noted in a memo: "NIH and NSF [National Science Foundation] individuals with whom Drs. Berg and Yanofsky talked did not see anything amiss in Stanford seeking such [patent] development. (In fact, the people at NSF had good words to say about our licensing program.) It was thus concluded that Stanford should proceed with development in its normal fashion."[53]

But the patent application had for some time not been "normal"; it had already moved beyond usual OTL routine. NSF was to take a back seat to the National Institutes of Health on the patent issue, and the NIH was soon to hedge on its affirmation of Stanford's patenting effort. From this point on, high-level Stanford officials were to be instrumentally involved in the patent issue; patenting in the area of recombinant DNA was seen as politically sensitive and at the same time as critical to the commercial development of the technology. If not handled astutely in regard to the biohazards controversy, the effort to commercialize the technology could turn into a political liability for Stanford and UC and for the NIH as administrator of the recombinant DNA guidelines and provider of research funds.

UNREST IN THE ACADEMIC COMMUNITY

In June 1976 questions regarding Stanford's patent application were openly voiced in a public forum. The occasion was a symposium at MIT on genetic engineering attended by eight hundred people, including Cohen and Boyer, the press, and those opposed to recombinant DNA research. It was one of many contentious events that summer, including the Cambridge City Council's fiery deliberations on recombinant DNA experimentation at Harvard and MIT. In this politically charged atmosphere, participants remarked on persistent rumors of Stanford's attempt to patent recombinant DNA technology and asked whether anyone in attendance could speak to the matter. Boyer remembers the tension of the situation: "[Stanley and I] gave talks, and people were jumping up and yelling, 'Is it true you're patenting recombinant DNA? How can you do that?'" Sensing all eyes focused on him, Cohen made the agonizing walk to the podium while trying to gather his thoughts for a response. Intensely uncomfortable, as he later privately acknowledged, he nonetheless managed to assuage anxiety by arguing, contrary to Reimers's contention, that a patent on recombinant DNA technology would provide a means to control its commercial devel-

[53] Reimers to "File—Gene Transplant," 9 Apr. 1975, S74-43, Correspondence 1974–1979, OTL Archives. An anonymous *Isis* referee remarked that the National Science Foundation began to emphasize technology transfer in this period. Hence it is no surprise that the agency supported Stanford's position.

opment.[54] This was a position that Reimers and other university adminstrators were soon to reject explicitly.

Cohen was in the spotlight for another reason. In 1975 he had become a scientific advisor to Cetus Corporation, a young Bay Area company that wanted to acquire expertise in recombinant DNA. It was not the propriety of Cohen's consultant position per se that was at issue: Stanford policy in the 1970s described consulting as a privilege beneficial to both individual faculty members and the university as long as it did not interfere with academic responsibilities. What raised concern in Cohen's case was the fact that he was an inventor on a Stanford patent application and at the same time a paid consultant for a company seeking a license on the invention being patented. He tried to reassure critics by arguing that he expected to be able "to effectively separate my relationship with Stanford as the Inventor, from my relationship with Cetus as a scientific consultant."[55] It was a fine—if not impossible—line that Cohen attempted to draw between Cohen the scientist, Cohen the inventor, and Cohen the corporate consultant. Patenting and licensing efforts constituted a process in which science, invention, and business were intertwined. Attempts to draw boundaries between the three interlocking realms were artificial and ultimately futile, as the emergence of a DNA-based biotechnology industry in the next decade was repeatedly to demonstrate. The problem that Cohen sought to solve on an individual basis and that Stanford and UC administrators faced at the institutional level was how to uphold academic standards of free inquiry and open communication while at the same time supporting the privatization and commercial development of university discoveries. This question would be at the heart of academic interaction with commercial biotechnology from the 1980s on.

THE POTENTIAL FOR PROFITS AND PROBLEMS

In May 1976 Reimers forwarded a draft of his plan for licensing the Cohen-Boyer technology to Mark Owens, his counterpart at the UC Board of Patents. The plan outlined potential commercial applications in a number of industrial areas, including human and animal pharmaceuticals, industrial enzymes, and agriculture. The draft contained sizable subsections devoted to "the biological hazard" and "the public relations hazard." It made manifest how closely the process of commercialization and the politics of the biohazard controversy were intertwined. Yet in July—contrary to historic arguments in university patenting—Reimers made it clear that the patent was not regarded as a means to control in the public interest the invention's use by industry:

> Stanford and the University of California . . . cannot . . . by a license agreement, legislate morality, nor prevent a licensee from conducting research in an area of potential hazard, nor prevent an accident by a licensee in releasing a biologically hazardous substance. It does appear reasonable, however, to seek from licensees, prior to issuing a license, an expression of their

[54] Boyer interview by Hughes, 27 July 1994, draft, p. 169 (quotation); and unattributed memo to file, 11 June 1976, S74-43, Correspondence 1974–1979, OTL Archives. For an account of the Cambridge, Massachusetts, and other local initiatives for regulation see Krimsky, *Genetic Alchemy* (cit. n. 8), pp. 294–311; and the Recombinant DNA Controversy Oral History Collection at MIT (cit. n. 42).

[55] "Policy on Consulting by Members of the Academic Council: Principles and General Standards," 11 Mar. 1977, and Richard W. Lyman, [Stanford University] President, to Members of the Academic Council, 18 Mar. 1977: Kornberg Papers, SC359, Box 5, Folder: 1977, Green Library, Stanford; and Cohen to Reimers, 14 June 1976, S74-43, Correspondence 1974–1979, OTL Archives (quotation).

> understanding of the potential hazards involved and their agreement to take precautions to conform with both law, good sense, common ethics, and the NIH guidelines.[56]

Neither Stanford nor NIH had the legal authority, the capacity, or the wish to regulate industry compliance with the NIH guidelines—which, after all, did not apply to industry in the first place.

There was yet another complication: Reimers learned from the U.S. Patent Office that claims on the recombinant organisms themselves, the so-called product claims, were for the time being unlikely to be allowed. As a consequence, the two universities filed a new patent application on 17 May 1976 that sought to protect only the basic Cohen-Boyer process and omitted the product claims. Second and third patent applications for the biological transformants—the cells genetically modified by the introduction of recombinant DNA—were being held in abeyance. "Product claims on new 'bugs' [microorganisms] are doubtful," Reimers explained, "although GE is pursuing coverage for their oil-eating bug in the courts." He alluded to the now-famous *Diamond v. Chakrabarty* case, in which General Electric sought to patent a living entity, a microorganism constructed to degrade crude oil. The case eventually reached the Supreme Court. Until the justices came to a decision, the U.S. Patent Office refused to consider patent applications claiming living organisms. Ananda Chakrabarty, the scientist who had developed the microorganism, did not use recombinant DNA technology to construct it. Nonetheless, *amicus curiae* briefs filed in the case, including one written by Genentech legal counsel, made reference to the implications of the decision for the commercial application of genetic engineering and the future viability of young biotechnology companies.[57] The question of the patentability of living organisms was of obvious significance to those interested in commercial exploitation of recombinant DNA.[58]

GENENTECH: CONTENDER FOR A PATENT LICENSE

Beginning in the spring of 1976, when Genentech was being formed, company president Robert Swanson became a persistent contender for license rights to the Cohen-Boyer

[56] Reimers to Mark Owens, 27 May 1976, and "Licensing Plan," draft, 14 May 1976: CU-6, UC (System), Office of Technology Transfer, Box 52, Folder: "Science & Technology, rDNA research," Bancroft Library, UC Berkeley; and Reimers to File S74-43, "Recombinant DNA Process," 17 July 1976, S74-43, Correspondence 1974–1979, OTL Archives (quotation).

[57] "Cohen-Boyer Application" [draft], serial no. 687,430, filed: 17 May 1976, CU-6, UC (System), Office of Technology Transfer, Box 52, Exhibit Book III, Bancroft Library, UC Berkeley (new patent application); Reimers to "Distribution," 15 Nov. 1976, S74-43, Correspondence 1974–1979, OTL Archives; and *Diamond v. Chakrabarty*, 447 U.S. (*United States Supreme Court Reports*), 303, 100 S.Ct. (*Supreme Court Reporter*) 2204 (1980), pp. 2204–2214. For a history of this case see Kevles, "*Diamond v. Chakrabarty* and Beyond" (cit. n. 15), pp. 65–79. *Amicus curiae* briefs were filed by nine organizations, including the University of California, the American Patent Law Association, the Pharmaceutical Manufacturers Association, the American Society of Microbiology, and Genentech, all of which had a stake in industrial application of the new genetic technologies. As Sheldon Krimsky has implied, the justices must have been aware of the commercial context and impact of their decision: Krimsky, "The Profit of Scientific Discovery and Its Normative Implications," *Chicago-Kent Law Review*, 1999, *75*:15–38. I thank an anonymous referee for calling my attention to this article.

[58] In October 1981 academic biologists and patent attorneys concerned with intellectual property rights in biotechnology met to explore the practical impact of the *Chakrabarty* decision on biological science and patent law. The resulting publication is David W. Plant, Niels J. Reimers, and Norton D. Zinder, eds., *Patenting of Life Forms* (Banbury Report 10) (New York: Cold Spring Harbor Laboratory, 1982). The impact of *Chakrabarty* and other intellectual property legislation and decisions, as well as the new tools provided by biotechnology, were of prime interest to the seed industry. See Frederick H. Buttel and Jill Belsky, "Biotechnology, Plant Breeding, and Intellectual Property," *Sci., Technol., Hum. Val.*, 1987, *12*:31–49.

process. He insisted in a flurry of letters and visits to Reimers and Opalka that license rights were critical to the young company's survival. Genentech needed the value represented in owning relevant license rights as a means to attract corporate investors. On 19 April, not two weeks after Genentech had been incorporated, Swanson proposed to Stanford and UC officials that the universities grant the company nonexclusive worldwide rights to use the licensed technology to produce "any product covered by the Licensed Technology" and exclusive rights to produce polypeptide hormones. Swanson's request for worldwide rights was moot because, as already noted, Stanford was precluded by law from filing for foreign rights to the invention. In exchange for an exclusive license, Swanson offered the two universities equity interest in Genentech in the form of four thousand shares of common stock. It was an early sign of the intimate relationship that commercial biotechnology was to create with academic institutions.[59] Reimers appreciated the damaging effect that a decision to issue only nonexclusive licenses might have: "This of course means that Genentech will not obtain its desired exclusive, that we forego equity and a possible substantial front payment for an exclusive, and it may mean that Genentech as a viable company cannot survive." Nonetheless, Reimers could not give Swanson the answer he wanted: "the jury was still out," he told him, in regard to a final decision about Stanford's licensing plan. Nonexclusive licensing was generally held to be viable only when inventions were revolutionary or broadly enabling.[60] It was becoming increasingly apparent that the Cohen-Boyer invention was in precisely this category.

CONSULTING THE NIH DIRECTOR

In 1976 Stanford officials sought counsel at the highest levels of university governance and the federal biomedical hierarchy by bringing the patent issue to the attention of Stanford's board of trustees and the director of NIH. In June Robert Rosenzweig, Stanford Vice President of Public Affairs, wrote to NIH Director Donald Fredrickson asking for advice as to whether Stanford should continue to seek patent protection on the Cohen-Boyer work. Rozenzweig acknowledged the political and ethical problems tied to the Cohen-Boyer patent application but couched his argument mainly in economic terms:

> It is a fact that the financing of private universities is more difficult now than at any time in recent memory and that the most likely prediction for the future is that a hard struggle will be required to maintain their quality. . . . To put the point as precisely as I can, we cannot lightly discard the possibility of significant income [from patent licenses] that is derived from activity that is legal, ethical, and not destructive of the values of the institution.[61]

[59] Boyer and Robert A. Swanson to "Gentlemen, Stanford University, University of California," 19 Apr. 1976; Swanson to Opalka, 28 Apr. 1976; and Opalka to Swanson, 10 May 1976: 74-134-1, Folder: "Cohen-Boyer Exploitation," UC OTT Archives. The long-standing collaboration between university scientists and the pharmaceutical industry predates the similarly close relationship in DNA-based biotechnology. For a history of the former see John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America* (Baltimore: Johns Hopkins Univ. Press, 1988). For histories of biotechnology see Kenney, *Biotechnology* (cit. n. 16); and Sheldon Krimsky, *Biotechnics and Society: The Rise of Industrial Genetics* (New York: Praeger, 1991).

[60] Reimers to Robert Augsburger, 19 July 1976, and Reimers to File S74-43 Recombinant DNA, 2 Aug. 1976, S74-43, Correspondence 1974–1979, OTL Archives. On nonexclusive licensing see Dueker, "Biobusiness on Campus" (cit. n. 39), p. 497.

[61] For Stanford's attempts to solicit guidance see Reimers to Rodney Adams, 8 Apr. 1976, S74-43, Correspondence 1974–1979, OTL Archives; and Reimers to Owens, 27 May 1976, CU-6, UC (System), Office of Technology Transfer, Box 52, Folder: "Science & Technology, rDNA," Bancroft Library, UC Berkeley. Rosenzweig's letter to Donald Fredrickson is reproduced in Watson and Tooze, *DNA Story* (cit. n. 34), p. 499; for the quotation see Robert M. Rosenzweig to "Those Interested in Recombinant DNA," 4 June 1976, S74-43, Correspondence 1974–1979, OTL Archives.

Rosenzweig's focus on patent-as-moneymaker was a new notion in university patenting in the United States, one that the Cohen-Boyer patent was to usher in and establish as a prime justification for patenting in academia.

Pursuant to its Institutional Patent Agreement with NIH, Stanford did not need additional permission from the government to file for a patent. Nonetheless, because of this patent's political sensitivity, Rosenzweig had decided to seek counsel in Washington. Fredrickson was fully enmeshed in problems related to recombinant DNA. In light of the biohazards issue and concern that patents in the field might inhibit scientific communication, an important question was whether NIH patent policy should be revised and more rigorous procedures established for patenting in the area of recombinant DNA. The fact that the NIH guidelines were scheduled for official release in late June, ending the sixteen-month research moratorium, served to increase tensions.[62] Could Fredrickson, as head of the federal agency issuing the guidelines, also support Stanford's efforts to obtain proprietary rights on recombinant DNA technology? Critics held that the patenting and licensing of recombinant DNA risked expanding to industry the sphere of action in which biohazards might arise.

Fredrickson had learned that the University of Alabama and a number of other universities were following Stanford's lead in filing for patents on discoveries in molecular biology. It was therefore imperative to resolve the political, ethical, and intellectual property protection issues raised by the Cohen-Boyer patent application and others to follow in biotechnology. To garner advice, Fredrickson began to consult various government and professional organizations. These deliberations were occurring during a period of extensive congressional reappraisal of federal patent and technology transfer policies prompted by concern over the flagging American economy and declining technological competitiveness. Because questions relating to Stanford's patent application were interwoven with unsettled federal policy regarding intellectual property rights in government-sponsored research, it would be almost two years before Fredrickson gave Stanford an answer.[63] Meanwhile, the Cohen-Boyer patent application and others involving recombinant DNA were stalled in the U.S. Patent Office, awaiting resolution of federal patent policy deliberations and a Supreme Court case.[64]

By March 1977, the California Assembly was considering a tough bill to regulate all laboratories in the state that practiced recombinant DNA technology. A number of mea-

[62] Fredrickson to Rosenzweig, 2 Mar. 1978, S74-43, Correspondence 1980–1982, OTL Archives. For a personal view of the problems facing Fredrickson at this time see D. S. Fredrickson, "A History of the Recombinant DNA Guidelines in the United States" (1979), in Watson and Tooze, *DNA Story*, pp. 396–399.

[63] For Fredrickson's efforts to solicit advice see, e.g., Fredrickson to Robert Carow, Association of American Medical Colleges, 7 Sept. 1976, CU-6, UC (System), Office of Technology Transfer, Box 52, Folder 2, Bancroft Library, UC Berkeley; and Fredrickson to Members of the Recombinant Advisory Committee, 27 Aug. 1976, CU-6, UC (System), Office of Technology Transfer, Box 52, Folder: "Science & Technology, rDNA Research." According to Nelkin, before 1980 patent policy regarding federally funded research was "in a state of confusion," with twenty-six different patent policies in effect at government agencies. The Bayh-Dole Act of 1980 provided a uniform federal patent policy designed to encourage commercial development of government-supported research. Nelkin, *Science as Intellectual Property* (cit. n. 13), pp. 13–14.

[64] In an effort to encourage rapid dissemination of information concerning recombinant DNA Research, the U.S. Patent Office in January 1977 instituted procedures intended to speed up review of related patent applications. In April the procedures were withdrawn as untimely in view of ongoing congressional consideration of recombinant DNA research legislation. Pending a decision on the patentability of recombinant organisms and plasmids, the patent office subsequently suspended review of applications claiming them until the issue was resolved. Thomas Kiley, "Patent and Political Shock Waves of the Biological Explosion," in *Proceedings of the Southwestern Legal Foundation Patent Law 17th Annual* (New York: Bender, 1979), pp. 253–285, esp. pp. 264–265.

sures with similar intent were before Congress, other state legislatures, and local government bodies. Although Stanford as an institution took no official position on the pending legislation, Berg, Cohen, Kornberg, and others on campus, as well as scientists elsewhere, were mounting an active opposition. The lobbying effort, one of the largest ever waged over a technical issue before Congress, helped to persuade legislators that the scientific and commercial benefits of genetic engineering outweighed its potential risks. Berg, now convinced that genetic engineering posed no real risk and opposed to giving government control of the science, argued forcefully against regulatory legislation at any governmental level and for "the tremendous opportunities afforded by the recombinant DNA methodology."[65]

COMMERCIAL PROSPECTS BEGIN TO CARRY THE DAY

A critical event in turning the tide of congressional opinion was Genentech's demonstration in the fall of 1977 of the feasibility of using recombinant DNA methodology to create in bacteria human proteins virtually identical to the naturally occurring forms. The successful production of the hormone somatostatin, which Genentech announced at a press conference in November, was presented as validating commercial application of the technology. "Molecular biology," Boyer declared to the media, "has reached the point where it can become involved in industrial applications." Boyer, whose image was to appear on the cover of *Time Magazine* in 1981, was one of the most visible proponents of capitalizing on molecular biology to make products of commercial use. (See Figure 4.) Cohen, more circumspect, continued to portray himself as respecting the traditional view of science as a communal endeavor.[66]

Berg and Philip Handler, president of the National Academy of Sciences, immediately announced the somatostatin achievement at U.S. Senate hearings on genetic engineering, calling it "a scientific triumph of the first order." The announcement was interpreted both in the Senate and in the media as indicating the exciting commercial prospects of applied biotechnology. As *Chemical and Engineering News* commented: "The success of the California researchers, both Handler and Berg declare, is a vindication of the utility of recombinant DNA research which should further defuse a tiny group of scientific critics who claim that the technique is potentially dangerous to laboratory workers and the public."[67]

Participants in the Senate hearings not only witnessed the biohazard issue being down-

[65] Paul Berg to Sen. Harrison Schmitt, 5 Jan. 1979, in Watson and Tooze, *DNA Story* (cit. n. 34), pp. 389–391. For the proposed California legislation see Assembly Bill No. 757, 3 Mar. 1977, introduced by the Committee on Health, copy in Cohen Personal Correspondence, Biohazard Collection, Stanford; and David Perlman, "Tough Rules on Creating New Forms of Life," *San Francisco Chronicle,* 4 Feb. 1977, p. 1. For scientists' federal lobbying efforts see "Testimony by Paul Berg," Subcommittee on Science, Technology, and Space, [U.S. Senate], 2 Nov. 1977, draft, Paul Berg Correspondence, SC 358, Accn. 90-020, Box 1, Folder: "Senate Testimony," Green Library, Stanford; Cohen's Senate testimony, in *Hearing before the Subcommittee on Health of the Committee on Labor and Public Welfare,* U.S. Senate, 94th Cong., 22 Apr. 1975 (Washington, D.C.: Government Printing Office, 1975), pp. 3–12; and Arthur Kornberg to the Honorable Paul N. McCloskey, 8 Aug. 1977, Kornberg Papers, SC 359, Box 3, Folder: "Genetic Engineering," Green Library, Stanford.

[66] "A Commercial Debut for DNA Technology," *Bus. Week,* 12 Dec. 1977, pp. 128, 132. The 9 Mar. 1981 cover of *Time Magazine* reads: "Shaping Life in the Lab: The Boom in Genetic Engineering: Genentech's Herbert Boyer." On Cohen's self-portrayal see David Dickson, "Inventorship Dispute Stalls DNA Patent Application," *Nature,* 1980, *284:*388.

[67] "Testimony by Paul Berg," 2 Nov. 1977; and "Human Gene in *E. Coli:* It Works!" *Chemical and Engineering News,* 7 Nov. 1977, p. 4.

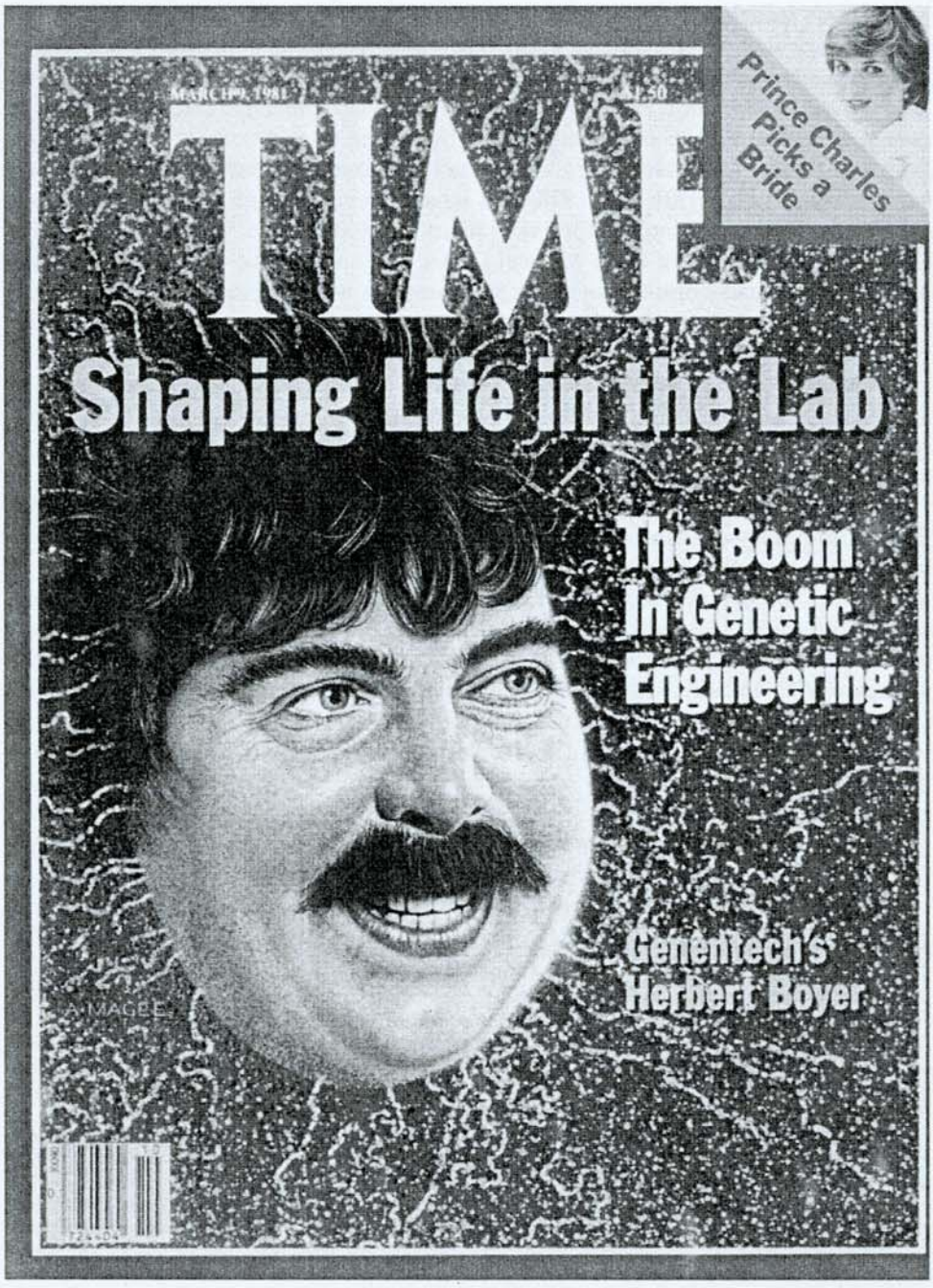

Figure 4. *Herbert W. Boyer on the cover of* Time Magazine, *9 March 1981. At the time Boyer was Professor of Microbiology and Biochemistry at the University of California, San Francisco, and cofounder of Genentech. Photograph courtesy of TimePix.*

played; they saw the ground being prepared for further industrial exploitation. The official report on the hearings was billed as "the first systematic effort to examine the issues that are likely to arise in the regulation of future large-scale commercial applications of recombinant DNA techniques." Although safety was still a discussion point, government and private-sector support of industrial expansion was described as a necessity if the United States had any hope of maintaining its leadership in the new genetic technologies.[68]

In the end, all federal bills to regulate recombinant DNA research died in Congress, in large part because legislators, heavily lobbied by a scientific coalition working through the American Society for Microbiology, recognized the value of the technology as a boost for the American economy. In July 1978 NIH issued a revised set of guidelines that eased restrictions on experiments; further relaxations were shortly to follow. In September Genentech and the City of Hope Medical Center announced to the media the production of recombinant human insulin, an accomplishment that was interpreted as the dawning of a new era of commercial biotechnology.[69] The waning of the recombinant DNA controversy loosened a constraint that had dominated Stanford's patenting and licensing strategy and complicated the process of commercialization. Although the biosafety question did not disappear from the public debate and has recently been revived with regard to genetically modified crops, it was fast losing force in the United States as a serious obstacle to mounting commercial pressures.[70]

Despite Stanford's repeated requests for guidance, it was not until March 1978 that Fredrickson finally announced the NIH position on intellectual property rights in recombinant DNA research. After consulting "a broad range of individuals and institutions on this matter," he had decided that no special procedure should be instituted for patent applications on such inventions. Fredrickson also gave Stanford permission to proceed with its licensing effort, though with the proviso that the licensed company "provides assurance of compliance with the physical and biological containment standards set forth in the [NIH] Guidelines in any production or use of recombinant DNA molecules under the license." Compliance, however, was to be voluntary; neither NIH nor Stanford had or wanted legal regulatory authority over industry.[71] There was no mention of an alternate enforcement mechanism.

Although the patent application was still stalled at the U.S. Patent Office pending the

[68] *Recombinant DNA Research and Its Applications,* Oversight Report by the Subcommittee on Science, Technology, and Space of the Senate Committee on Commerce, Science, and Transportation, August 1978 (Washington, D.C.: Government Printing Office, 1978), pp. iii (quotation), 37.

[69] For accounts of the derailing of U.S. federal legislation, including the role of Stanford and UCSF scientists, see Wright, *Molecular Politics* (cit. n. 8), pp. 256–278; and Krimsky, *Genetic Alchemy* (cit. n. 8), pp. 312–337. For an assessment of NIH guideline revision at this time see Wright, *Molecular Politics,* pp. 281–311. On the production of recombinant human insulin see "First Successful Laboratory Production of Human Insulin Announced," 6 Sept. 1978, Corporate Communication Division Files, Genentech, Inc., South San Francisco, California; "Human Insulin: Seizing the Golden Plasmid," *Science News,* 16 Sept. 1978, pp. 195–196; and Matt Clark with Joseph Contreras, "Making Insulin," *Newsweek,* 18 Sept. 1978, p. 93.

[70] Internationally, political concern regarding recombinant DNA waxed and waned at different rates in different countries. Maureen McKelvey notes that as the biohazard issue waned in the United States after mid 1977, the media in Sweden increasingly described the risks of the technology: McKelvey, *Evolutionary Innovations: The Business of Biotechnology* (Oxford: Oxford Univ. Press, 1996), pp. 109–113. For the situation in Great Britain see Wright, *Molecular Politics.* Although perhaps most noticeable in biotechnology, other academic sciences in the United States, such as those related to the electronics industry, were also experiencing greater commercial activity in the 1980s. For differences in industry growth patterns at this time see "A Comparison of the U.S. Semiconductor Industry and Biotechnology," Appendix C, *Commercial Biotechnology: An International Analysis* (Washington, D.C.: Office of Technology Assessment, Congress of the United States, 1984), pp. 531–540.

[71] Fredrickson to Rosenzweig, 2 Mar. 1978, S74-43, Correspondence 1980–1982, OTL Archives; and Reimers, "Tiger by the Tail" (cit. n. 5), p. 39 (on compliance).

Supreme Court decision in *Chakrabarty,* Reimers wasted no time in proceeding to finalize a licensing plan. A definitive decision had been made: Stanford would issue nonexclusive licenses on the Cohen-Boyer technology. Since Cohen had designated his royalties for research and education, Reimers pointed out that Stanford could claim that two-thirds of any future net income from the patent would be used for these purposes. This strategy was intended to deflate critics of university patenting and to mollify the coauthors of the original DNA cloning papers. Helling and Morrow nonetheless continued to refuse to sign a release of claim to inventorship. Like Paul Berg, Helling felt that no university should be allowed to claim rights on a technology as fundamental and broadly applicable as recombinant DNA. Their protest in the end was fruitless. Not only was the first patent to issue with only Cohen and Boyer as inventors; the second and third patents did likewise, even though the question of inventorship cropped up again in the 1980s.[72]

In June 1980 the Supreme Court held in *Chakrabarty* that living organisms engineered by man were potentially patentable under existing statutes. In a landmark 5-4 decision, the justices ruled that Chakrabarty's microorganism was not a product of nature but, rather, a novel invention of his own ingenuity and thus patentable subject matter. This was a critical ruling for commercial biotechnology: the patent system henceforth was to be used for securing property rights on all manner of living organisms and their components. Partly on the strength of the decision, Genentech went public on 14 October. Within minutes after the opening bell, frantic investors on the New York Stock Exchange purchased one million shares and the stock price rose from $35 to $89. Without an immediately marketable product, Genentech had in a few short hours raised $38.5 million, and Boyer and Swanson had gained a paper profit of $60 million on an initial investment of $500 each.[73] A period of speculative frenzy over genetic engineering had begun.

The decision in *Chakrabarty* released for review a stream of patent applications involving living organisms that had been held up in the patent office awaiting the opinion.[74] The Cohen-Boyer application was among them. On 2 December 1980 the U.S. Patent Office issued patent 4,237,224 on a "Process for Producing Biologically Functional Molecular Chimeras."[75] In early August 1981 Stanford announced the availability of licenses for the Cohen-Boyer invention, describing it as the start of "an unprecedented effort to license the entire genetic engineering industry for use of its basic scientific technique." By 15 December seventy-two companies had licensed the Cohen-Boyer technology, which Reimers described in his promotional material as "the basic tool needed in genetic engineering."[76] Each company had paid a license issue fee of $10,000, with another $10,000 due

[72] On the decision about licensing see Reimers to Massy, 26 Jan. 1979, 74-134-1, Folder: "Cohen-Boyer, Exploitation," UC OTT Archives; for Helling's views see Joel Gurin and Nancy E. Pfund, "Genetic Engineering: Bonanza in the Bio Lab," *Nation,* 1980, *22:*542–548, on p. 544; on later questions about inventorship see Marjorie Sun, "Stanford's Gene Patents Hit Snags," *Science,* 1982, *218:*868–869.

[73] Kevles, "*Diamond v. Chakrabarty* and Beyond" (cit. n. 15), pp. 70–71; and Boly, "Gene Merchants" (cit. n. 28), p. 79.

[74] By one account, 114 patent applications involving living organisms were held up in the patent office awaiting the Supreme Court's decision in *Chakrabarty:* Krimsky, "Profit of Scientific Discovery" (cit. n. 57).

[75] The legal status of the 1980 patent and the two pending patents was repeatedly debated. See, particularly, Albert P. Halluin, "Patenting the Results of Genetic Engineering Research: An Overview," in *Patenting of Life Forms,* ed. Plant *et al.* (cit. n. 58), pp. 67–126; and Jorge Goldstein, "A Footnote to the Cohen-Boyer Patent and Other Musings," *Recombinant DNA Technical Bulletin,* Dec. 1982, pp. 180–188.

[76] Stanford University News Service, advance for release Monday, 3 Aug. 1981, S74-43, Correspondence 1980–1982, OTL Archives. In an effort to encourage early licensing, Stanford offered credit to firms taking out licenses by 15 Dec. 1981 of five times the initial payment of $20,000 against future royalties on resulting products.

on 1 February 1982. By the latter date total license income would be $1,420,000, a sign of the financial windfall to come.[77]

CONCLUSION

This essay has shown that the universities' hard-won success in securing the recombinant DNA patent was tied to events at the national level. By the time the patent was issued, the cautionary approach to science and technology of the early 1970s was giving way under the Reagan administration to a view that science-based technology was central to economic growth. Congress was taking steps to encourage technological development through such means as deregulation, corporate financing, and tax relief, and federal agencies such as the National Science Foundation were developing programs designed to promote collaborations between universities and industry. Biotechnology figured among the high-technology areas that the government sought specifically to encourage for commercial development.[78] The field's promise as a new and profitable sector of the American economy was among the reasons for passage of the Bayh-Dole Act of 1980, which gave universities the right and incentive to hold patents on innovations arising from federally funded research. The increase in university patenting after the act went into effect in 1981 is one measure of its success in encouraging academic entrepreneurialism. In 1980 universities held title to approximately 150 patents; by 1990 the number had grown to 1,600. According to one historian of biotechnology, the new economic and political climate in Washington was "the crucial factor" in intensifying corporate competition after 1979 to apply recombinant DNA commercially.[79]

In tracing the patent history, we have seen interest in the industrial application of the new technology overtake earlier safety and regulatory concerns. The course patent prosecution took reflects a shift in national political focus from protectionism to technological and industrial expansionism. At first a prime consideration for those formulating patenting and licensing strategy, the biohazard issue was by the end of the decade losing out to forces in government, academia, and industry propelling recombinant DNA technology

[77] Roger G. Ditzel, [UC] Patent Administrator, to [UC] Vice President William B. Fretter, 18 Dec. 1981, 74-134-1, Folder: "Cohen, S. et al.," UC OTT Archive ($1,420,000). Media coverage of Stanford's announcement of the licensing plan focused on its moneymaking potential and its importance for the production of new biological products. See, e.g., Charles Petit, "Stanford, UC Plan to Get Rich on Gene Patent," *San Francisco Chronicle,* 1 Aug. 1981, p. 7; Victor Cohn, "Stanford Moves to Speed Use of Gene Splicing," *Washington Post,* 3 Aug. 1981, p. A6; and David Dickson, "Stanford Sells Gene-Splicing Licenses," *Nature,* 1981, *292:*405. The three patents expired as a unit on 2 Dec. 1997, having earned over $250 million in royalties and license fees: Floyd Grolle, former licensing officer of the Cohen-Boyer patents, Stanford OTL, personal communication, 8 Oct. 1998.

[78] On the new attitude under the Reagan administration see David Dickson, *The New Politics of Science* (New York: Pantheon, 1985), p. 5. On efforts to encourage collaborations see Lois S. Peters and Herbert I. Fusfield, "Current U.S. University/Industry Research Connections," in *University-Industry Research Relationships: Selected Studies* (Washington, D.C.: National Science Foundation, 1982), pp. 1–162; and Dorothy Nelkin and Richard Nelson, "Commentary: University-Industry Alliances," *Sci., Technol., Hum. Val.,* 1987, *12:*65–74 (part of a special issue called "Private Appropriation of Public Research"). On governmental interest in biotechnology see *Commercial Biotechnology* (cit. n. 70), esp. pp. 8–21.

[79] Wright, "Recombinant DNA Technology" (cit. n. 8), p. 345. Wright's article considers additional factors contributing to the intensification of competition in commercial biotechnology in this period. On the Bayh-Dole Act see "Technology Transfer Comes of Age: Bayh-Dole Fifteen Years Later," summary report, Annual Meeting of the Association of University Technology Managers, Ottawa Carleton Research Institute, 1995, Sect. 3: "The Bayh-Dole Act and What It Means," pp. 4–6; the 1980 and 1990 figures are on p. 6. The report can also be found online: http://strategis.ic.gc.ca/SSG/tf00159e.html. Between 1980 and 1990 the number of patent applications on NIH-funded inventions increased by almost 300 percent: Krimsky, "Profit of Scientific Discovery" (cit. n. 57).

toward privatization and commercial exploitation. By late 1980, when the patent was issued, the NIH guidelines had been weakened to the point of virtual dismantling. The single brief provision in the patent license agreement asking licensees voluntarily to comply with the NIH guidelines is symbolic of the national shift away from social control of technology.[80]

In regard to the commercialization of molecular biology, it is clear from the historical record that the Cohen-Boyer patent was not critical to the initial diffusion and earliest industrial exploitation of recombinant DNA. The technology's potential for tailoring life processes more precisely to mankind's practical needs had been quickly apparent to Cohen and Boyer and others familiar with its capabilities. Hence the protection and exclusivity traditionally provided by a patent had not been required to induce companies to take up the technology and develop it for commercial purposes. As this essay has described, Genentech and a number of large corporations and small genetic engineering firms were utilizing recombinant DNA technology in commercial processes well before the first patent was issued in December 1980. For the entrepreneurs and business executives of these enterprises, what was paramount was the availability of a revolutionary new tool with a variety of exciting practical applications.[81] Despite the murkiness of patent law as applied to genetic engineering, individuals founded biotechnology companies, academic scientists and others became corporate executives and employees, established corporations developed capacity in recombinant DNA technology, and investors sank capital into the new endeavors. Although those running the first companies knew the special importance of owning and controlling intellectual property in biotechnology, the viability and legal standing of patents in the new field was generally seen as a problem to be worked out over time as legal experience and precedents were established. In this vein, the president of Biogen, one of the new biotechnology companies, concluded: "We're going to be aggressive in applying for patents, but we don't know what they're worth and we won't depend on them. We'll depend on fast running."[82]

What then is the importance of the first Cohen-Boyer patent for commercial biotechnology? The answers lie not so much in the realm of hard facts—although there were some, as the patent was widely licensed and gave signs of becoming a real moneymaker for Stanford and UC—as in the realm of business psychology, legal precedent, and agency.

[80] For the circumstances of the political decline of the recombinant DNA controversy in the United States and Britain see Krimsky, *Genetic Alchemy* (cit. n. 8), pp. 283–293; and Wright, *Molecular Politics* (cit. n. 8), pp. 337–437. On the weakened NIH guidelines see Wright, "Recombinant DNA Technology," p. 338. In June 1980 the Recombinant DNA Advisory Committee, responding to corporate concern over possible disclosure of trade secrets during the review process, revised the guidelines to provide for protection of proprietary information at this stage: Nelkin, *Science as Intellectual Property* (cit. n. 13), p. 29. On the advice of NIH, the clause in the Cohen-Boyer patent license agreement concerning the NIH guidelines was further softened. Instead of "Licensee agrees to comply with the physical and biological containment standards set forth in the NIH Guidelines . . . ," the wording was changed to "Licensee specifically expresses its intent to comply . . .": William P. O'Neill to Bernard Talbot, M.D., Associate Director, NIH, 24 Apr. 1981, S74-43, Correspondence 1980–1982, OTL Archives.

[81] Another lure was of course the chance to make a personal fortune. In a parody of the so-called central dogma of molecular genetics—DNA (makes) RNA (makes) protein—one wag remarked: DNA (makes) RNA (makes) money: Usher Fleising and Alan Smart, "The Development of Property Rights in Biotechnology," *Culture, Medicine, and Psychiatry,* 1993, *17:*43–57, on p. 53.

[82] Hal Lancaster, "Profits in Gene Splicing Bring the Tangled Issue of Ownership to the Fore," *Wall Street Journal,* 3 Dec. 1980, p. 1. Eighteen biotechnology firms were founded in 1980, thirty-three in 1981: Kenney, *Biotechnology* (cit. n. 16), p. 140. For a quantitative assessment of linkages between biological faculty at American universities and the biotechnology industry between 1985 and 1988 see Sheldon Krimsky, James G. Ennis, and Robert Weissman, "Academic-Corporate Ties in Biotechnology: A Quantitative Study," *Sci., Technol., Hum. Val.,* 1991, *16:*275–287.

Stanford's well-publicized prosecution of the patent in the face of major political and legal obstacles had attracted a diverse audience in academia, government, and industry that regarded its fate as suggestive of the commercial prospects of recombinant DNA. The mere fact that the patent was issued, despite formidable setbacks, provided a psychological boost for those interested in commercial biotechnology. But its effects on the field were more than momentary. Its broad claims on the recombinant DNA process required any company practicing the technology in the United States to license it or risk litigation.[83] Following within six months of the *Chakrabarty* decision affirming the patentability of living organisms, issuance of the Cohen-Boyer patent served to reinforce confidence that commercial biotechnology had a future and was a sound investment opportunity. The patent's wide scope and dominant position and the immediate success of its licensing plan were stabilizing and reassuring factors in the heady but uncertain business and legal environment of the pioneering years of an emerging biotechnology industry.

Investors and other interest groups had few economic indicators by which to estimate the potential success of the biotechnology start-up firms formed from the late 1970s on and often touted with considerable hyperbole. What these companies mainly offered in lieu of immediate products were scientific and technological concepts and expertise whose merit the investment community had difficulty in assessing. Consequently, a firm's ability to instill confidence in its capacity to generate, sustain, and protect intellectual property was critical to its ability to attract investors and fund its research and development. The encouragement and reassurance that the Cohen-Boyer patent and, to a lesser extent, other early patents in biotechnology contributed was significant in the formative stage of a commercial field in which proprietary rights to scientific processes and products were central and critical. In this vein, a cofounder and former CEO of a biotechnology company remarked: "all the early patents were viewed as positive, because if you couldn't protect this intellectual property, then people were not going to invest in the field. So it was the fact that patents would issue, even if they were in your way, that gave people confidence that the field would be able to create value."[84]

The patent history also shows the continuity of concerns that had accompanied commercial ventures in academia for much of the twentieth century. Lederberg's and Kornberg's fear that Stanford's patenting effort would induce secrecy in science was far from new.[85] The university's new president, Donald Kennedy, worried in 1980 that growing

[83] In late 1981 Reimers set up a $200,000 fund from royalties for use if litigation ensued: KRP [Kent R. Peterson] to DXK [Donald Kennedy], "End-Game on Cohen-Boyer," 2 Dec. 1981, S74-43, Correspondence 1980–1982, OTL Archives. The Cohen-Boyer patents were never litigated. By August 1982, a year after Stanford advertised the availability of licenses, Stanford reported income to the two universities of $1.4 million: "Genetic Engineering Patent Delayed," News Bureau, Stanford University Medical Center, 5 Aug. 1982, S74-43, Correspondence 1980–1982, OTL Archives.

[84] Edward E. Penhoet, quoted in "Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders," oral histories with Hugh A. Andrade, David P. Holveck, and Edward E. Penhoet conducted in 1998 and 1999 by Sally Smith Hughes, Regional Oral History Office, Bancroft Library, Univ. California, Berkeley, 2001, p. 102. In addition to its role as a confidence booster, the Cohen-Boyer patent and its licensing plan have served as models for structuring other broad patents and their licensing plans. For a recent example see Alan Dove, "Opinions Evolve on Kauffman Patent," *Nature Biotechnology*, 2000, *18*:373.

[85] Kornberg's reservations about commercial ventures in biotechnology were and are restricted to university patenting. In 1980 he, Paul Berg, and Charles Yanofsky cofounded the private DNAX Research Institute of Molecular and Cellular Biology, which was acquired by Schering-Plough in 1982. For histories of DNAX see the Kornberg oral history (cit. n. 36); and Kornberg, *Golden Helix* (cit. n. 52). For a study of specific patent claims in the monoclonal antibody field and their implications for "a subtle but significant shift in the political economy of science and technology" see Michael Mackenzie, Peter Keating, and Alberto Cambrosio, "Patents and Free Scientific Information in Biotechnology: Making Monoclonal Antibodies Proprietary," *Sci., Technol., Hum. Val.*, 1990, *15*:65–83, on p. 65.

campus interest in patenting and other commercial activities threatened to create "a proprietary atmosphere" that could jeopardize the academic tradition of free scientific inquiry and open communication.[86] It was a concern to be argued with new immediacy in the 1980s as a biotechnology industry highly dependent on basic academic science began to coalesce, enticing increasing numbers of academic scientists and their universities to capitalize on the new opportunities. (See Figure 5.) With the increase in patenting in biotechnology, new power relationships were established through intellectual property rights that determined who had access to specific information and who did not.[87] The public and scientific media in the 1980s featured countless stories on the benefits and risks of increased patenting in academia and the various research arrangements being created between universities and industry, with biotechnology in most cases providing the illustrative examples. Policy at American research universities was reformulated after 1980 largely to accommodate greater faculty and institutional involvement in outside business concerns and efforts to secure proprietary rights.[88]

In the practical realm, the patent served as inspiration and model for other universities, setting a pattern for and spurring growth of more efficient and profitable patenting and licensing operations on American campuses.[89] The instability of government research support, which Rosenzweig had noted in the mid 1970s, was to continue in the next decade to motivate universities to commercialize their research inventions and seek greater private-sector investment. Just as Cohen overcame his initial hesitations over patenting, so would many other biomedical scientists and institutions reinterpret their contract with society in ways that allowed the growing commercial movement in American biomedicine to proceed.

The patent and its two companions of 1984 and 1988 were instruments in the transformation of perceptions and policy regarding commercial activity in academia. No longer was a university patent perceived primarily as a means for technology transfer or for

[86] [Robert] Beyers, "Free Inquiry Must Be Rule in Research," [Stanford] *Campus Report,* 5 Nov. 1980, *13*(7):1, 18. The implications of the concept of science as property were of wide interest in science in the 1980s. An examination of the subject by a committee of the American Association for the Advancement of Science resulted in Nelkin's 1984 summary in *Science as Intellectual Property* (cit. n. 13).

[87] Although close university-industry collaborations in chemistry and other applied fields have occurred since the nineteenth century, the two spheres remained largely distinct and interaction was restricted. A recent development is the creation of an "interphase" in which academic, industrial, and sometimes third parties intermingle. For discussion and examples see Gaudillière and Löwy, eds., *Invisible Industrialist* (cit. n. 19): "Introduction" to Pt. 3, pp. 298–299; Vivien Walsh, "Industrial R&D and Its Influence on the Organization and Management of the Production of Knowledge in the Public Sector," *ibid.,* pp. 301–344; and Nelly Oudshoorn, "Shifting Boundaries between Industry and Science: The Role of the WHO in Contraceptive R&D," *ibid.,* pp. 345–368, esp. p. 361.

[88] One of many occasions at which university policy regarding interactions with industry was considered was the 1982 Pajaro Dunes, California, conference arranged by Stanford president Donald Kennedy and attended by corporate leaders and university presidents. For a contemporary account see Barbara Culliton, "Pajaro Dunes: The Search for Consensus," *Science,* 1982, *216:*155–156, 158. Among 1980s articles on patenting in academia, with a focus on biotechnology, see Jeffrey L. Fox, "Can Academia Adapt to Biotechnology's Lure?" *C&EN [Chem. Eng. News],* 12 Oct. 1981, pp. 39–81; Culliton, "The Academic-Industrial Complex," *Science,* 1982, *216:*960–962; and David Blumenthal, Michael Gluck, Karen Seashore Louis, Michael A. Stoto, and David Wise, "University-Industry Research Relationships in Biotechnology: Implications for the University," *ibid.,* 1986, *232:*1361–1366. As anyone in current touch with the media knows, the debate about the effect of increased patenting and other forms of commercial activity in academia continues. See, e.g., Michael A. Heller and Rebecca S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *ibid.,* 1998, *280:*698–701.

[89] "On loan" from Stanford, Reimers spent 1985–1986 as director of the Technology Licensing Office at MIT, where he "reformed existing licensing office and developed staff." A major impetus for the appointment was the success of the Cohen-Boyer patents. Resumé in Reimers oral history, p. 50.

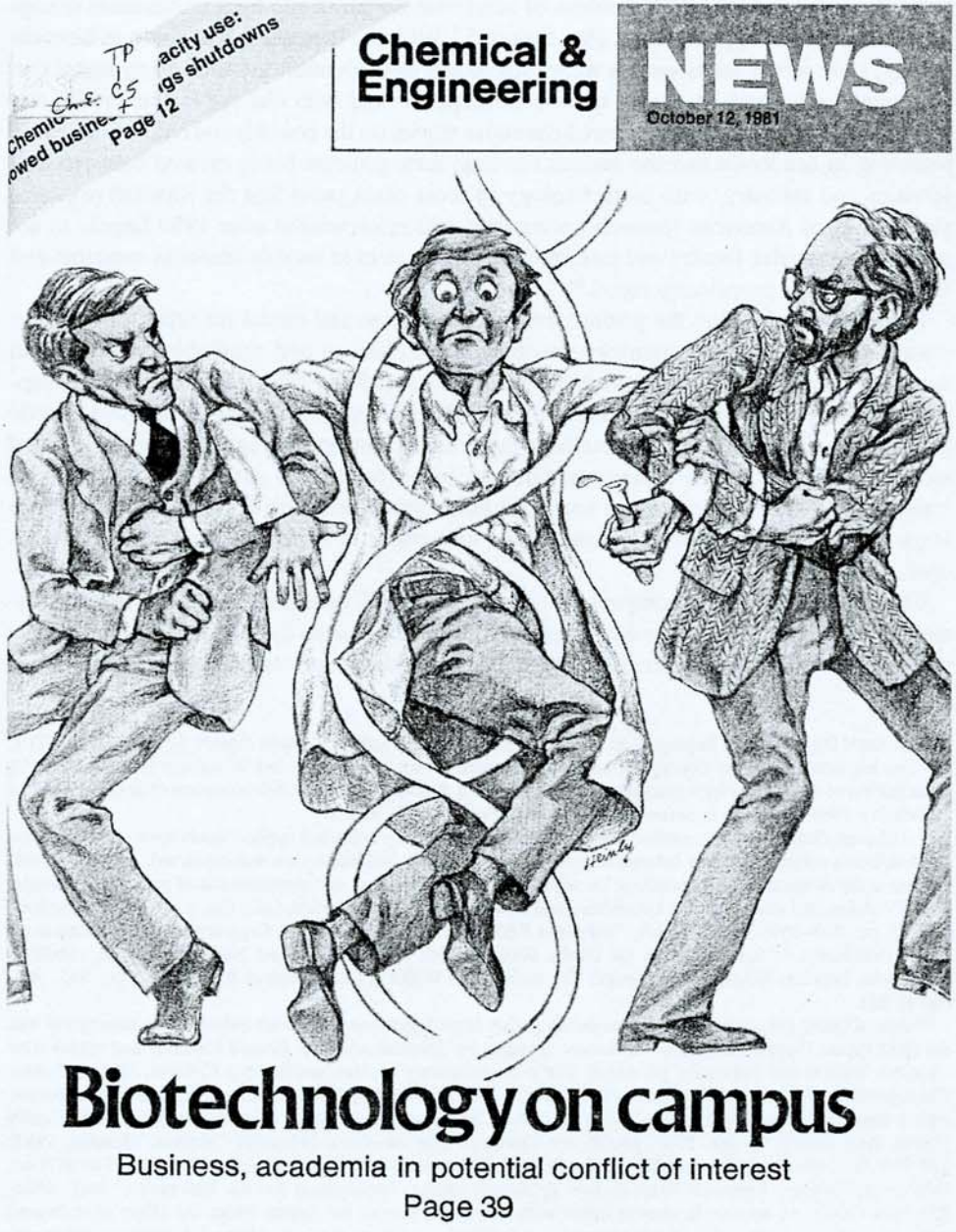

Figure 5. *Illustration on the cover of* Chemical and Engineering News, *1981, depicting an academic scientist in a DNA helix being tugged in two different directions by a university scientist and a businessman.*

controlling use of an invention; in the 1980s patenting became a way for universities and scientists to make money. Biological knowledge was being privatized, commodified, and given economic value in addition to its value as a cultural good. But for those willing to look beyond their resounding commercial success, the Cohen-Boyer patents also carried subtle seeds of concern regarding the effect of patenting and licensing on the culture and norms of academic research. They were thus simultaneously agents of attitudinal and institutional change and harbingers of ethical issues that were to accompany the accelerating commercialization of academic biomedicine and the rise of the biotechnology industry in the years ahead.[90]

[90] For an account of subsequent commercialization of the biological sciences and its effect on the culture and ethos of academic biology see Krimsky, "Profit of Scientific Discovery" (cit. n. 57).