Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in the History of the Biological Sciences and Biotechnology

Thomas D. Kiley

GENENTECH LEGAL COUNSEL AND VICE PRESIDENT, 1976-1988, AND ENTREPRENEUR

With Introductions by
Rebecca S. Eisenberg
James W. Geriak

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2000 and 2001

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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It is recommended that this oral history be cited as follows:

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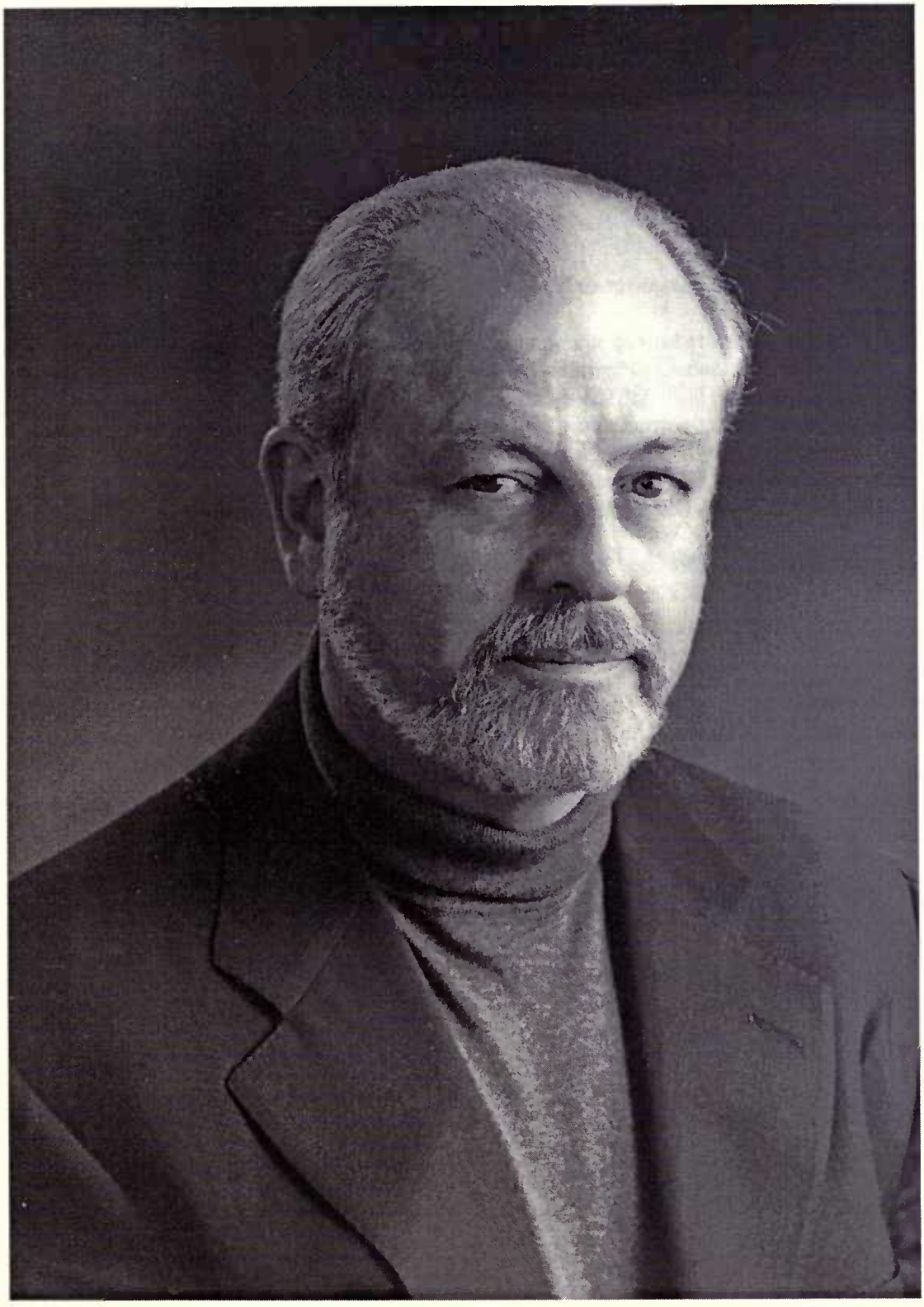

Thomas D. Kiley, 2002

photo credit: Doerr Studios

Cataloguing information

Thomas D. Kiley (b. 1943) Patent Attorney/Entrepreneur

Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur, 2002, xi, 217 pp.

Education in chemical engineering, law; early experiences as patent examiner and patent solicitor; intellectual property trial lawyer, Lyon & Lyon; outside legal counsel to Genentech, 1976-1980; vice president and general counsel, Genentech, 1980-1988: Genentech's IPO, 1980; *Diamond v. Chakrabarty* Supreme Court case; recombinant DNA; commercialization of biotechnology; intellectual property; R&D clinical partnerships, patenting and licensing; Genentech-University of California legal relationships; Bayh-Dole Act, 1980; Genencor; Geron; Intermune Pharmaceuticals; NIH-DOE Joint Committee on the Human Genome, 1992; comments on Herb Boyer, Dave Goeddel, Robert Swanson and others.

Introductions by Rebecca S. Eisenberg, Professor, University of Michigan Law School; and James W. Geriak, Partner, Orrick, Herrington & Sutcliffe, Irvine, CA.

Interviewed in 2000 and 2001 by Sally Smith Hughes for the Program in the History of Biosciences and Biotechnology, Regional Oral History Office, The Bancroft Library, University of California, Berkeley.

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Genesis of the Program in the History of the Biological Sciences and Biotechnology

In 1996 The Bancroft Library launched the Program in the History of the Biological Sciences and Biotechnology. Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. Yet, although the university is located next to the greatest concentration of biotechnology companies in the world, Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as Bancroft's director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists and the pioneers who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences and generates constant public interest and controversy is vital for a proper understanding of science and business in the late twentieth and early twenty-first centuries.

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history and archival program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in the History of the Biological Sciences and Biotechnology was given great impetus by Genentech's generous pledge to support documentation of the biotechnology industry.

Thanks to these generous gifts, Bancroft has been building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library networks; and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library Web pages.

Oral history as a historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

Emerging Themes

Although the oral history program is still in its initial phase, several themes are emerging. One is "technology transfer," the complicated process by which scientific discovery moves from the university laboratory to industry where it contributes to the manufacture of commercial products. The oral histories show that this trajectory is seldom a linear process, but rather is influenced by institutional and personal relationships, financial and political climate, and so on.

Another theme is the importance of personality in the conduct of science and business. These oral histories testify to the fact that who you are, what you have and have not achieved, whom you know, and how you relate have repercussions for the success or failure of an enterprise, whether scientific or commercial. Oral history is probably better than any other methodology for documenting these personal dimensions of history. Its vivid descriptions of personalities and events not only make history vital and engaging, but also contribute to an understanding of why circumstances occurred in the manner they did.

Molecular biology and biotechnology are fields with high scientific and commercial stakes. As one might expect, the oral histories reveal the complex interweaving of scientific, business, social, and personal factors shaping these fields. The expectation is that the oral histories will serve as fertile ground for research by present and future scholars interested in any number of different aspects of this rich and fascinating history.

Location of the Oral Histories

Copies of the oral histories are available at the Bancroft, UCSF, and UCLA libraries. They also may be purchased at cost through the Regional Oral History Office. Some of the oral histories, with more to come, are available on The Bancroft Library's History of the Biological Sciences and Biotechnology Website: http://bancroft.berkeley.edu/Biotech/.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2002

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[1]The three criticisms leveled at oral history also apply in many cases to other types of documentary sources.

October 2002

ORAL HISTORIES ON BIOTECHNOLOGY

Program in the History of the Biological Sciences and Biotechnology

Paul Berg, Ph.D., "A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry," 2000

Mary Betlach, Ph.D., "Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory," 2002

Herbert W. Boyer, Ph.D., "Recombinant DNA Science at UCSF and Its Commercialization at Genentech," 2001

Thomas J. Kiley, "Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur," 2002

Arthur Kornberg, M.D., "Biochemistry at Stanford, Biotechnology at DNAX," 1998

Fred A. Middleton, "First Chief Financial Officer at Genentech, 1978-1984," 2002

Thomas J. Perkins, "Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995," 2002

"Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders" (Hugh D'Andrade, David Holveck, and Edward Penhoet), 2001

Niels Reimers, "Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents," 1998

William J. Rutter, Ph.D., "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco," 1998

Robert A. Swanson, "Co-founder, CEO, and Chairman of Genentech, 1976-1996," 2001

Oral histories in process:
Brook Byers
Stanley Cohen
Chiron Corporation
Roberto Crea
David Goeddel
Herbert Heyneker
Irving Johnson
Dennis Kleid
Arthur Levinson
G. Kirk Raab
William J. Rutter, vol. 2
Richard Scheller
Axel Ullrich
Keith R. Yamamoto

INTRODUCTION by Rebecca S. Eisenberg

I first met Tom Kiley at a deposition in San Francisco in 1981. Although I can't recall the witness, I remember the setting vividly. We were in a conference room in the law offices of Heller, Ehrman, White & McAuliffe, high above the ground in the heart of the financial district, facing north across the San Francisco Bay. It was a clear day, and it seemed that there were almost as many lawyers in the room as there were sailboats in the water. As a new associate in the firm, I had just been added to a growing litigation team at work on an interesting new case in the office involving rights in a cell line that had been used in the course of cloning an interferon gene. On one side of the dispute was our client, Hoffmann-La Roche, and its research partner, Genentech. On the other side was my alma mater, the University of California. Hoffmann-La Roche, having agreed to absorb the full cost of any potential damage award in order to remove a potential cloud on Genentech's initial public offering of stock, had assumed control of our side of the litigation.

Kiley, as counsel for Genentech, and I, as the junior member of the legal team for Hoffmann-La Roche, were seated at one end of the table, with many lawyers separating us from the witness and court reporter. It was the first deposition I had ever attended, and I was unsure of my role. Although Kiley was then still a young lawyer himself, at the time he struck me as a seasoned professional in a position of great responsibility, and I glanced his way from time to time in the hope of learning something about how to behave. He held a pad of paper in his lap, as did most of the others at the table, and he appeared to be absorbed in meticulous note-taking. He evidently noticed that I was watching him, and tipped his notepad toward me. Was this a question from co-counsel? Eager to cooperate, I turned my full attention to what he had written, and found - a rather good sketch of the Bay, with sailboats and Angel Island in the foreground, and the Marin Headlands beyond.

This was my first clue that Tom Kiley was a breed apart from the other patent lawyers I was meeting. His gaze extended far beyond the matter at hand, and he was having a lot more fun than they were.

In fact, as general counsel for a technology-based start-up company, Tom Kiley was pioneering a new role for patent lawyers. In the early 1980s, patent law was an arcane specialty within the legal profession that few lawyers knew (or cared to know) anything about. Although it was common for large companies, such as pharmaceutical firms, to employ their own in-house patent lawyers, the prestigious role of general counsel was typically filled by a generalist with a broader background in corporate and commercial law.

For a technology-based startup, however, the first legal priority was to implement an intellectual property strategy that would permit the firm to capture the value of its R&D. A clever patent lawyer could work with scientists and entrepreneurs to stake out a patent position that would dominate future developments, strengthening the firm's hand in negotiations with research partners and offering a promise of future profits to entice investors. Patent lawyers were typically the first lawyers these firms needed and identified, but not every startup was lucky enough to find a patent lawyer with a broad enough strategic vision to make the smartest opening moves.

As the first general counsel of Genentech, Tom Kiley had to be willing to look beyond the walls of the firm to see what opportunities and hazards lay on the horizon. He had to devise persuasive legal arguments for establishing the patentability of a technology that many nonscientists saw as arrogant meddling with natural forces and fraught with hazards to the public. He had to foresee the potential

commercial applications of inventions that were far removed from the marketplace, and justify patent claims that would cover those applications. He had to untangle and resolve conflicts over proprietary rights in the ambiguous zone between academic and commercial research. He had to work out an allocation of legal rights in the innovative partnerships his client was forging with pharmaceutical firms and nonprofit institutions that would permit research to go forward, while reserving for Genentech a substantial piece of the action. He had to pick his battles, decide which rights to keep and which to bargain away, all the while looking down the road toward the goal of building Genentech into a fully integrated pharmaceutical company.

Some twenty years later, Kiley is in a position to look back on his own early strategic moves and see how they played out. Few biotechnology firms of that era have fared as well as Genentech, and it is hard to imagine that the firm could have prospered without the guidance of an aggressive and creative patent strategist.

Yet as he reflects upon the past twenty years, Kiley does not emerge as an uncritical champion of the patent system. Quite the contrary, he offers sobering reflections on the ways that the patent system has failed the biotechnology industry. He fears that, "We're cluttering up the landscape with such a dense thicket of patents that before long I fear companies will be caught like flies in amber and unable to move in any direction." Noting that "there is a dark side to the patent system," he worries that "to the extent we insist on patenting the very tools of science, the very raw materials on which scientists operate, we run the risk of standing the patent system on its head and discouraging rather than promoting the creation of new things." He condemns as "one of the great evils of the patent system" the availability of broad "composition of matter" claims that give inventors control over all uses of newly invented materials, rather than limiting their claims to the uses that they know and disclose in their patent applications. He laments that "the Patent Office is not a very effective filter against bad patents," and condemns the creation of the Court of Appeals for the Federal Circuit as "a very big mistake." By foreclosing the dialogue and debate that goes on among different circuits in other fields, Kiley observes that the concentration of patent jurisdiction in a single patent court has caused patent jurisprudence to become "constipated" and "unduly pro-patent, with the result that in some respects it's fair to say America is choking on patents and innovation is stifled by them."

This is hardly the party line of the patent bar. But perhaps the trained focus of patent lawyers on the particular matters at hand has distracted them from the broader landscape of innovation. Kiley's perspective is surely an enlightening one for anyone who believes that a successful patent system is one that generates new products, not merely new patents. To evaluate the patent system according to that metric, one must look outside the window.

Rebecca S. Eisenberg
Robert & Barbara Luciano Professor of Law
University of Michigan Law School

Ann Arbor, Michigan
September 9, 2002

INTRODUCTION by James W. Geriak

Many persons of Irish heritage are blessed with an active intellect and innate sense of fun. Tom Kiley possesses each of these qualities in abundance. Thus, knowing him as I have for the past 30 years has been both intellectually invigorating and extraordinarily enjoyable.

A few anecdotes are worth relating, but first a bit of history. Tom and I met when we were recruiting him out of law school for our law firm, Lyon & Lyon, in 1968. On that occasion, I took Tom out to dinner and when he observed that he had offers from other firms for a few more thousand dollars than our firm was offering, I shocked him by encouraging him to take those offers if money was the only thing that was important to him. At the time, it was our deliberate policy to peg our starting salaries at a level slightly less than the highest salaries available to avoid just that, namely, bringing in people for whom money had a disproportionate importance in life. Tom's quick mind immediately went to work on this issue and, in short order, he announced, "You're right, I accept." One of the ironies of our age is that Tom, by reason of his willingness to take risks and as a result of his participation in building Genentech into one of the world's leading biotechnology companies, he has become very well-off indeed.

Tom and I practiced law together for approximately ten years during which most of our activity involved litigating patent infringement cases. The cases involved such cerebrally challenging subject matter as polymers cross-linked by ionizing radiation, pharmaceuticals, and other cutting-edge technology. However, two cases stand out in my memory. The first was the so-called "permanent press patent litigation" in which our client Koratron sued the entire apparel industry and some of the fabric industry for infringing a patent directed to the manufacture of permanent press clothing. The subject matter was humble, but the stakes were enormous. There were 16 opposing parties, including such industry behemoths as Levi Strauss and Deering Milliken. Because Koratron's adversaries alleged that it had committed antitrust violations, our client also retained the late-great Moses Lasky, with whom we worked, shoulder to shoulder, for seven years. Moses Lasky could be a dominant figure, but he met his match in young Tom, whom he often referred to as the "Mysterious Mr. Kiley" when their intellects did not entirely mesh. Tom and Moses became lifetime friends.

The other case of ours worth mentioning is that in which Miss Universe Inc., proprietor of the Miss U.S.A. pageant, sued the promoters of the Miss Nude U.S.A. pageant for trademark infringement. This case required no intellect whatsoever, but did provide the opportunity for Tom to indulge his whimsy, which he did with enthusiasm, including having his picture taken with Miss Nude U.S.A., whose only attire was a bouquet of roses (Tom was fully clothed). This picture was prominently displayed in Tom's office during his time at Lyon & Lyon.

In 1976, an opportunity knocked when Bob Swanson informed Tom Kiley that Bob was starting a biotechnology company which would attempt to make commercial use of certain biotechnology breakthroughs achieved by two scientists named Boyer and Cohen. This company was Genentech. Initially, Tom represented Genentech as a member of Lyon & Lyon and was a key participant in one of the single most important legal-economic events of the 20th century. That was the issue of whether developments in biotechnology involving genetic engineering, cloning and the like could properly be patented, which became a burning issue in the late 1970s. The issue was debated endlessly in the public and scientific press and, inevitably, became the subject of litigation. The United States Supreme Court finally granted *certiorari* in *Diamond v. Chakrabarty* and the stage was set for a Supreme Court determination on this issue. It was well

recognized that the case was of enormous social, scientific, and economic importance, which resulted in the Supreme Court being deluged by briefs from *amici curiae* ("Friends of the Court"). Such a brief was filed on behalf of Genentech and its sole author was Tom Kiley. The case was decided by a 5-4 margin in favor of patentability of biotechnology subject matter and the way was paved for investment in this remarkable new technology, which has benefitted mankind so enormously. It is of great relevance here that the majority decision of the Supreme Court was plainly guided by Tom Kiley's amicus brief. Court decisions are often simply an adoption of the reasoning presented in a brief submitted to the Court and so it was in *Diamond v. Chakrabarty*. Thus, Tom was, in effect, the "Sixth Justice" who wrote for the majority.

The bonds formed among those who try lawsuits together are among the most durable and so it has been for Tom and me. It has been a pleasure to watch Tom enjoy, more than most, the material rewards of his success. However, for this long-time friend, there has been and always will be a great sense of loss occasioned by Tom's decision to leave private practice 20 years ago. We would have had a rollicking good time litigating together for the last two decades.

James W. Geriak
Partner, Orrick, Herrington & Sutcliffe

Irvine, CA
November 5, 2002

INTERVIEW HISTORY--Thomas D. Kiley

These interviews with Tom Kiley covering his education and several careers focus on the middle years when he was at Genentech, the first company founded on the sole basis of genetic engineering. First as outside counsel (1976-1980), then as vice president for corporate affairs and general counsel (1980-1988), he was in a position to influence Genentech policy during the spectacular yet precarious years of the young company. In addition, because Genentech was the first company off the block in what came to be known as the biotechnology industry, Kiley, armed with a keen legal intellect, experience in intellectual property law, and a persona unburdened by timidity, was in the right place at the right time to shape early patents, licensing agreements, and other business arrangements in biotechnology. He was thus instrumental in setting legal precedents for the budding industry. His subsequent career as founder, director, and consultant of several public and private companies is herein briefly sketched.

The oral history process began with Kiley's donation of two cartons of documents dating from his Genentech career which I thoroughly researched for the interviews and will deposit in The Bancroft Library. I also pulled upon the documents I have collected and interviews conducted since the biotechnology oral history project began in 1992. Mr. Kiley's oral history is the first in the series to be focused on the legal aspects of biotechnology and hence represents an important addition to the documentation of an industry in which intellectual property protection is central.

Five interviews, each two to four hours long, were recorded at the Bancroft Library between August 9, 2000 and March 12, 2001. We each came to the interview sessions with lists of topics, which proved to be remarkably similar, proposed for discussion. At first businesslike and in control, Kiley soon warmed to the give and take of the interview process. He was called to testify in two major legal cases in biotechnology during the period in which the interviews were recorded. In addition he knew that all interview transcripts, as with all others funded by the Genentech gift, were to be reviewed by Genentech legal counsel solely for legal content. The reader should be aware of these circumstances having the potential to affect interview content.

Sally Smith Hughes, Ph.D.
Historian of Science and Project Director

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
July 2002

Regional Oral History Office
Room 486 The Bancroft Library

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BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name THOMAS DANIEL KILEY

Date of birth APRIL 29, 1943 Birthplace SWISSVALE, PA.

Father's full name THOMAS ALOYSIUS KILEY

Occupation BUSINESS EXECUTIVE Birthplace PITTSBURGH, PA.

Mother's full name FRANCIS KILEY (nee WATT)

Occupation HOMEMAKER Birthplace PINE GROVE MILLS, PA.

Your spouse/partner NANCY LYNNE KILEY (NEE METHVEN)

Occupation HOMEMAKER Birthplace MONESSEN, PA.

Your children SEAN THOMAS, ALISON, RYAN PATRICK

Where did you grow up? ALISON PARK, PA.

Present community HILLSBOROUGH, CA.

Education B.S. (CH.E) 1965 PENN STATE UNIVERSITY
J.D. 1969 GEO. WASHINGTON UNIVERSITY

Occupation(s) PATENT EXAMINER, PATENT AGENT, PATENT ATTORNEY, V.P. GENERAL COUNSEL, V.P. CORP. DEVELOPMENT, CORPORATE DIRECTOR

Areas of expertise PATENT LAW, NEGOTIATION, CORPORATE GOVERNANCE

Other interests or activities TRAVEL, FLYFISHING, WING SHOOTING, READING, POETRY

Organizations in which you are active DIRECTOR OF GERON, INC., CELLGATE, INC., CONNETICS, INC.; MEMBER OF THE FAMILY, A PRIVATE CLUB

SIGNATURE Thomas D Kiley DATE: FEB. 10 2002

INTERVIEW WITH THOMAS D. KILEY

I FAMILY BACKGROUND AND EDUCATION

[Interview 1: August 9, 2000] ##[1]

Grandparents

Hughes: We're starting at the beginning of this saga with the family background of Thomas D. Kiley. Perhaps you'd start with a quick overview of your grandparents.

Kiley: My maternal grandfather, William Watt, ran a general store in Pine Grove Mills in the center of Pennsylvania. He and my grandmother, Jane Watt (née Neelan) then moved to Pittsburgh, where my father's parents lived. They were Timothy and Mary (née Bresnahan) Kiley. William, burdened with the necessity of feeding eight children, before long took his own life. Timothy and Mary had eleven children, of whom my father was oldest. Timothy was a timekeeper at United Engineering and Foundry Company, which made heavy equipment for the steel industry. My father (Thomas Aloysius) left home at sixteen (in 1925) over a dispute with his father. He wanted to invest some small part of his meager earnings in stocks, giving over the balance to support his brothers and sisters. Timothy wanted it all for that purpose. Never completing high school, Tom began as a clerk at United and ended life forty-five years later as director and vice president for purchasing.

Hughes: Your early life?

Kiley: I was born in 1943 and first raised in a duplex in Swissvale, Pennsylvania, just across the Monongahela River from the Homestead Works, the first plant built by United States Steel after Andrew Carnegie and J. Pierpont Morgan put that company together. Just upstream in Braddock, where I was born, was the J. Edgar Thomson Works, Carnegie's first mill. Coal smoke, now rare in my experience, still evokes nostalgia.

My mother Frances was a secretary at Union Switch and Signal Corporation. She married my father after he carried the engagement ring in his pocket for years, burned by the Depression, until he could pay it off. From then on she was a homemaker. It was a matter of pride for my father that his wife shouldn't "work." And he would buy nothing on credit.

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[1]## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

In 1949, we moved to a $14,000 home in the green surrounds of Pittsburgh. I had a typical childhood--baseball and bicycles, other sports, and student politics in high school, then I went off to college to study chemical engineering.

Higher Education and Early Experience in Patent Law

Undergraduate, Pennsylvania State University, 1961-1965

Hughes: Why chemical engineering?

Kiley: I think that happened for two reasons. First, my father, who hadn't gone to college and who had been Depression-raised told me if I insisted on a college education, then at least I should have one that gave me a trade that could feed me in hard times. He thought engineering would do that. And of course there was Sputnik, which made engineering a desired destination for a whole generation of us.

So off [I went] to Penn State in chemical engineering, where it developed either I wasn't old enough or mature enough to study chemical engineering--or made a mistake in joining a fraternity that made *Animal House* look like a ladies' tea party. I went from dean's list my freshman year into the fraternity [and] to below single digits in my quarterly grade points, and spent much of my undergraduate career digging myself out of that.

After I graduated, I learned that there was something called patent law that might let me satisfy my abiding interest in the law, an interest that was first inspired--like that of many lawyers--reading Louis Nizer's biography and stories of his trial experiences. I learned in patent law one could combine an interest in technology with an interest in law.

Hughes: That was your own discovery?

Kiley: Actually it came to my attention through a friend and co-worker of my father whose nephew was a recruiter for the United States Patent Office and who happened to mention that there were careers in patent law. I looked into it and applied to a number of law schools.

George Washington University Law School, 1966-1969

Kiley: I recall being turned down by George Washington University on the strength of my abysmal grade point average the same day I was offered a scholarship to Duquesne on the strength of outstanding scores on the law school aptitude test. The George Washington read was: lots of brains, but no energy. [laughter] I decided then and there that George Washington might be the better law school, and so I took a job in Washington and camped out on the doorstep of the dean of admissions until I got him to change his mind.

Hughes: How did you convince him?

Kiley: Persistence, and straight A's in my last undergraduate quarter.

Choosing the Law over Chemical Engineering as a Career

Hughes: What had turned you around?

Kiley: Rejection and having espied something that seemed more interesting to me than the highly empirical field of chemical engineering.

What turned me off about engineering were the lookup tables and the fudge factors. Not much seemed elegant about it as against physics or chemistry, and [it was] truly a trade. Unlike the pure sciences, in which you're not expected to make contributions until you've completed your doctorate, in engineering you are supposed to be a profit center from the time you graduate. So you spend your whole college career learning to be useful and little of it learning how to learn or broadening yourself.

Hughes: How did you arrive at that outlook? The message you said your father was giving you was, "Tom, if you've got to get an education, choose something that is practical, that will feed you."

Kiley: And good advice.

Hughes: Oh, yes! No doubting that, but chemical engineering would have done that.

Kiley: Well, if I was any good at it. [laughs] I think we all in our college years are trying to find ourselves and our metier and our forte and what turns us on. I had gone into a technology-based discipline because technology turned me on, but at least in my then state of development, the associated empiricism turned me off. I was still looking for great proofs and great principles, and indeed may have migrated toward the law with that unusually romantic idea in mind.

And of course law school satisfies because you get the sweep and breadth of legal history and legal logic. It's a rich history and a human history and a whole compendium of values and principles that are admirable. What they don't--or didn't in those days--teach you was all about the nitty gritty of patent law and the drudgery that can be associated with complex litigation. In any event, I enjoyed law school and found that I had a knack for taking the examinations and actually graduated second in my combined night and day class of 350 people.

Attraction to Patent Law

Hughes: Always headed towards intellectual property law?

Kiley: That is right. I had worked hard to get my modest degree in chemical engineering, and I wanted to get some benefit from it and at the same time satisfy my interest in the law. The more I learned of patent law, the more interesting it seemed to me.

Nowadays intellectual property has come to the fore in legal practice across the country as America has become more and more reliant on knowledge-based industries, while heavy industries have hollowed out and gone overseas. Where once the patricians of the silk stocking law firms would look down their long noses at what they referred to as the green-eyeshade boys in patent law, now they can't get enough of it because it influences so much of our industry and because the associated transactions and litigation are complex and expensive. And that draws lawyers like flies to honey. I just found it intellectually stimulating.

Examiner, United States Patent and Trademark Office, 1965-1967

Kiley: I worked my way through law school by being employed, first, as an examiner at the Patent Office in Washington, D.C.

Hughes: Was that position granted on the strength of your chemical engineering education?

Kiley: Yes. At that time, and even today, patent examiners are required to have a degree in engineering or the sciences. One goes through a several-week orientation called the "patent academy" in which one learns enough of the basics of patent law to make supervised judgments about the patentability of applications that are submitted to the Patent Office. So I did that for several years until, as was not uncommon then, I reached a point of diminishing returns and decided to go to the other side of the fence.

Patent Solicitor, E. I. du Pont de Nemours and Company, 1967-1969

Kiley: I joined the Washington law office of DuPont and for several years was a patent solicitor obtaining patents for DuPont--until graduation, and having graduated, off [I went] to the West.

II INTELLECTUAL PROPERTY TRIAL LAW, LYON AND LYON, 1969-1980

The Firm

Kiley: I joined a firm called Lyon and Lyon begun by Frederick Lyon in 1901. When I joined the firm, it was and it remained one of the largest intellectual property firms in the country and one that devotes itself largely to patent litigation, as against obtaining patents from the Patent Office. And so like major firms in New York, Chicago, Houston, and so on, it had a national practice, trying cases all over the country that had heavy technology content: trade secret theft, patent infringement, trade regulation, trademark infringement, and so on.

Hughes: Had you decided upon Lyon and Lyon mainly as a vehicle for bringing you West?

Kiley: Well, I was not well traveled until my law school graduation, and the West had its allure, largely synthetic as known to me: the home of Disneyland, Hollywood, and palm trees. I recall being surprised when I first came to Los Angeles and found there were no pueblos here. [laughter]

The real choice was between corporate and law firm employment. I was offered a position by Chevron here, by United States Steel in Pittsburgh, and so on. I had decided that I wanted to be a trial lawyer because that's what Louis Nizer was, and that's what Perry Mason was, and there ought to be a way, I thought, to be a trial lawyer and have all that fun and still indulge one's interest in technology. Patent law turned out to be it. And I must say that it's never lost its fascination for me. Intellectual property lawyers are technology junkies, if you will. They're technology voyeurs that get to look through lots of interesting windows. And I get to deal intimately with people involved in the business of creation, and derive all that [tape interruption] vicarious satisfaction without having to do the hard work of science. And that's just a kick.

Dealing with Scientists

Hughes: How did you like dealing with the scientists themselves?

Kiley: I had all the usual preconceptions about scientists that proved as phony as the whole notion of the priesthood of science that Jim Watson overthrew when he lifted the veil in his book, *The Double Helix*. Scientists are just like other people except they are more competitive than any trial lawyer I ever met, more competitive than most business men I have met, for the reason that in science you get no prizes for being the runner-up. If you're not first, you're nothing. The very notion of scientific research is to bring something forward that wasn't known before. Who's the second person to figure out Einstein's mass energy equivalence? No one knows, because he's nobody or she's nobody. So scientists are competitive. They tend to be very well traveled. They tend to be nonparochial in their viewpoint because the scientific community is a worldwide community, and altogether I love being around them, and I love looking over their shoulders.

First Court Appearance

Hughes: Well, go into more detail about what happened at Lyon and Lyon. It was your first opportunity to practice intellectual property law, right?

Kiley: In a manner of speaking. I was practicing intellectual property law when making my puerile judgements as a wet-behind-the-ears patent examiner about who was entitled a patent.

Hughes: That's on the other end of it.

Kiley: Yes. And then soliciting patents for DuPont, I was becoming a practitioner of sorts, but in terms of the trial practice, of course [I was] a complete novice as I came to Lyon and Lyon.

I will never forget my first court appearance. I was sent down to the district court house in Los Angeles with a very mundane task, to make a motion to get an extension of time within which to respond to discovery. Unfortunately the judge I had to make this application to was in the midst of trying the Pentagon Papers case. The judge's clerk informed him there was a motion that needed to be heard and the judge declared a recess in the trial. Four hundred members of the press turned around and looked at me expectantly. [laughter] I stood at the podium with my mouth feeling as if the Russian Army had just marched through it with their socks on and my stomach all aflutter. The judge said, "We'll take up that patent matter now." Four hundred members of the press stormed for the exit and the coffee machine and left me alone in court with the judge and his clerk.

Hughes: Your grand entrance.

Kiley: It's the fascination intellectual property law then held with members of the press.

Impact of Biotechnology on Intellectual Property Law

Kiley: Nowadays it's remarkably different, and I think that's due in no small part to the notoriety and celebrity of biotechnology and the many challenges that biotechnology has imposed on intellectual property law. Difficult questions spring up around issues emanating from ownership of life processes and living organisms and information encoded in our genes. There's a remarkable connection that the lay public makes with the life sciences that seems different in kind from the way they connect with other fields. There's something personal about the business we're in. There's something that's deeply felt by onlookers, and by all of us when you come right down to it.

Patent Litigation Cases

Kiley: To revert to Lyon and Lyon days, like any newly minted lawyer in the intellectual property field, I had to do my share of patent application work before I could be trusted with matters in litigation, but that came soon enough. I remember we represented a little California dressmaker that had invented permanent press clothing and had signed up several hundred companies around the world to pay royalties every time they made a pleated skirt--remember those?--or a pair of pants. And then some of those licensees decided to stop paying. Other companies were found that were infringing the patent. We gathered up eighteen of these companies and brought them here to San Francisco, as Moses Lasky[1] said, "Huffing and puffing to the judgment seat," and that was *Jack Winter v. Koratron.*

We had, over the course of two-and-a-half months, forty lawyers in a courtroom--eighteen cases consolidated for a single trial. "The invention of permanent press," we said to the court, "had lifted from the backs of American women the slave burden of ironing." [laughter] We sued Levi Strauss & Co., we sued Lee, Haggar, Farrah, Milliken, Burlington Industries--wonderful lawsuit from a lawyer's perspective, a real steak-and-cocktails case. That was my first experience with San Francisco and I loved it. I was very much a junior lawyer. I was the fifth man on a five-man trial team.

I recall one night returning to my hotel from dinner at Vanessi's to find a message that my wife Lynne had gone into labor and my daughter Alison [Kiley, now DeBord] was expected. In those days, you could still get a 3 a.m. flight to Los Angeles. I flew down and witnessed the birth of my daughter, stuck around for a few days, came back, and told the head of our trial team that I was the proud father of an eight-pound girl. "Oh," he said, "Mr. Kiley, were you gone?" [laughter]

The firm's litigation practice spanned the whole spectrum from the sublime to the absurd--

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[1]Then of Brubeck, Phleger, and Harrison, who led our trial team.

Kiley: --from the Civic engine technology of Honda to a veterinarian who claimed to have a cure for cancer and baldness; from representing the inventors of impact polystyrene to representing Miss Nude USA when she was sued for trademark infringement by Miss USA. Quite a diverse practice, and every case different from every other, which is the great thing about intellectual property law. You're always operating on something that by definition is new and different relative to other things, unlike trying the same whiplash case over and over and over again all your life.

It is the *sui generis* aspect of intellectual property law that makes it expensive. Every case requires a complete retrospective on the development of a whole field of technology so that inventions can be put into the context in which they arose when they're evaluated for patentability.

III GENENTECH, INC.: OUTSIDE PATENT COUNSEL, 1976-1980

First Encounter with Robert Swanson, June 1976

Hughes: Please describe your first encounter with Genentech.

Kiley: I was approached by Bob Swanson, a cofounder of Genentech, in mid-1976 shortly after he and Herb Boyer incorporated the company. Bob came to me seeking [legal] counsel at a time when he was Genentech's only full-time employee. The first entry in my daybook is in June 1976.

Bob got to me by a circuitous route. He used to like to tell the analysts and investment bankers he had identified me through Sherman and Sterling, a silk stocking New York law firm that represented his one-time employer, Citibank. He said that he approached Sherman and Sterling and asked them to identify the best patent lawyer in the western United States, and I suppose that was Bob's way of doing a patent brag about his company. Of course it's all apocryphal.

The truth is that Sherman and Sterling sent him across the street to a New York patent law firm, where I think he bounced down the letterhead until he came to a junior partner who evinced little interest in taking seriously a twenty-eight-year-old man who claimed to be en route to forming a major independent pharmaceutical company. That attorney called a young partner, Douglas Olson in my law firm, Lyon and Lyon in Los Angeles, whom he'd known from law school. My partner said later he held the phone away from his ear while speaking to Swanson on the esoteric subject of gene-splicing and said to himself, "Let's see. Kiley represents lots of these weirdos; I'll send Swanson to him." And from that came my representation and friendship with Bob Swanson.

Bob had me vetted by Art Riggs of the City of Hope National Medical Center [in Duarte, California]. Art is a scientist's scientist, and evidently Swanson believed that it would be important that Art be persuaded that I was the sort of lawyer with whom he could work.

Previous Experience with Intellectual Property in Biology

Kiley: I knew nothing of gene-splicing. The entire controversy over genetic engineering, the whole Asilomar conference, were things that I had been completely oblivious to. Nevertheless, I managed to tap dance my way through a conversation with Dr. Riggs and made something of my having represented the Nucleic Acid Research Institute of ICN Pharmaceuticals in intellectual property matters. Nucleotides are to DNA as pearls are to strings of pearls, and so that was the whole of my expertise in the area, coming into the representation of Genentech.

Hughes: Is there a story to your involvement with the Nucleic Acid Institute?

Kiley: No, it was a typical representation. I worked with their scientists, patented the products of their work. They were largely interested in slipping nucleotide analogues into the DNA of pathogenic organisms in order to disrupt their function. The only drug I recall having emerged from that is something called Ribavirin (TM), now approved for the treatment of a respiratory disease that commonly affects infants.

Hughes: Was that representation your first introduction to biology?

Kiley: I had some passing experience in biology, largely in areas having to do with diagnostic technology, immunoassay, things of that nature. But I must say that my only prior [educational] experience was a single three-credit course in undergraduate school that devoted little attention to esoteric subjects like DNA, and nothing to what we've come to know as molecular biology. It's not unusual, however, for patent attorneys to greet with open arms people from diverse disciplines. I think, over time, patent lawyers learn to become quick studies and extract from their clients what they need to know to do their jobs.

DNA Synthesis of Somatostatin

Commercial Application of Recombinant DNA

Hughes: Please carry the story with Art Riggs a little further.

Kiley: Well, Swanson began Genentech with the notion that the gene-splicing technique Boyer and Cohen had developed several years earlier [1973-1974] was ripe for commercialization. He had persuaded Boyer that was true. Said in another way, Boyer had validated to Bob that commercialization might be in the offing. So Genentech was founded with the notion that, first of all, it would make human insulin in *E. coli* from synthetic DNA.

Boyer had learned of a proposal by Riggs and [Keiichi] Itakura at the City of Hope National Medical Center to express in bacteria another hormone--one called somatostatin. Boyer explained to Swanson that DNA synthesis, that is, nucleotide by nucleotide synthesis of DNA, would be important in taking the gene-splicing technology forward. It was that

technology Riggs and Itakura proposed to bring to bear on somatostatin. Swanson wanted me to assist him in establishing an arrangement between Genentech and City of Hope under which the project would be funded at City of Hope, also funded at Boyer's laboratory at the University of California at San Francisco, working in collaboration with Riggs and Itakura; and to ensure that Genentech obtained, from the research it funded, the exclusive right to practice the resulting technology.

So my first act for Genentech lay in going out to the City of Hope, getting briefed by Riggs and Itakura on what was proposed, and then working with City of Hope counsel to establish the contract under which the work would be done.

Hughes: Did Riggs and Itakura have any experience with intellectual property law?

Kiley: None that was evident to me. And they'd had an unfortunate experience with other sources of funds: they had prepared a grant application and submitted it to the National Institutes of Health, seeking funding for the somatostatin project. That funding was denied them. The reviewers, I am told, said the proposal lacked scientific merit and that it could not be completed in the several years for which funding had been sought. I've always found it interesting that with a modicum of Genentech funding, $300,000 in all, the project was completed in nine months--and by the private sector.

As to whether the project had scientific merit, I am reminded that when it was completed, Boyer described to Paul Berg in general terms what had been done at a time [November 1977] when both Berg and Boyer were to testify to a subcommittee of the United States Senate. Berg in his remarks concerning the somatostatin achievement called it "astonishing." In similar testimony on that same day, Philip Handler, who was then president of the National Academy of Sciences, called it "a scientific triumph of the first order."

Once the somatostatin contract was in place, and a somewhat parallel agreement in place with the University of California to cover the Boyer end of the collaboration, I had little Genentech involvement in ensuing months--until success was in hand. And then I was obliged to scribble furiously to get patent applications on file in time for the Genentech announcement [in 1977] of the production of somatostatin in bacteria, which it made at a press conference in conjunction with the City of Hope.

Hughes: At that time, it was unusual in academic biology to announce a scientific discovery to the media before it was published.

Kiley: I believe at the time the press conference was held the paper was in press, and so the norms of science were conformed with. I don't recall a great deal about the press conference other than that the work was described to a half dozen or so reporters then in attendance. But what was most important about that to me and to the company was that it proved the principle that a human hormone--a human product--could be produced in bacteria, and so validated the company, and so led quickly to Eli Lilly's expression of interest in taking up the insulin project and funding that work in Genentech's hands.

Somatostatin to Demonstrate Proof of Principle

Hughes: Tell how Genentech's first effort was diverted from insulin to somatostatin.

Kiley: Well, Bob was very unhappy with Art Rigg's insistence that the somatostatin project precede the insulin work. Obviously insulin had a market. The market for somatostatin was speculative at best. To this day, recombinant somatostatin has not found a market application.

In the end, Riggs was right to insist we do somatostatin first. Somatostatin was adequate to demonstrate the principle, and in many ways more straightforward than insulin. Somatostatin is constituted by a single chain of fourteen amino acids. That meant that a relatively small piece of DNA would suffice to encode for the product. The days when DNA would rapidly be synthesized in automated devices were not yet upon us. Very few laboratories in the world had capability in synthesizing long strands of DNA. Itakura was among them. He had trained in the laboratory of Saran Narang in Canada; [Gobind] Khorana, later a Nobel laureate, had capability, but it was not widespread.

DNA synthesis then was a tedious and laborious task. Keichi set out to synthesize the fragments that were to be combined to form the DNA, forty-two nucleotides in all, encoding somatostatin. It took many, many months. Had the company pursued insulin first, it would have taken on a project that required three times as much DNA synthesis. Unlike somatostatin, insulin is a two-chain polypeptide, so it would have been necessary to synthesize both chains, then carry out their combination in bioactive form. And while that could well be done with the same notional technology, it represented substantially more work than I think the company had money for at the time. Far better to prove the principle with somatostatin and then use Lilly's money to make insulin. And in the event, that's what was done.

The Research Team and Its Approach

Hughes: Who was actually doing the work?

Kiley: At City of Hope, Riggs and Itakura--with a small group of other organic chemists, one of whom was Roberto Crea, who later joined the company. At the University of California at San Francisco, Boyer oversaw a group which included Paco Bolivar, Herb Heyneker, and a number of others whose names are lost to me, but who will appear as authors of the somatostatin publication.[1]

Hughes: What was the division of labor?

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[1]K. Itakura, R. Crea, T. Hirose, A.D. Riggs, H.L. Heyneker, F. Bolivar, and H.W. Boyer, "Expression in *Escherichia coli* of a Chemically Synthesized Gene for the Hormone Somatostatin," *Science* 198 (1977): 1056-63.

Kiley: The DNA fragments were synthesized by Itakura and his group. The synthetic plan was commented upon by the people in Boyer's lab, who had relatively more experience in ligating DNA into plasmidic DNA. The fragments were then assembled by the Boyer laboratory and put into the expression vector. The bacteria were transformed in the Boyer lab. That is, the plasmid bearing the somatostatin DNA was put into the bacteria. It was then sent down to the Riggs laboratory where, in an assay developed by Wiley Vail of the Salk Institute and made available to Riggs, one looked for somatostatin in the contents of the cell.

Hughes: Riggs and Itakura already had an association with Wiley Vail?

Kiley: I believe so. Unfortunately when they first looked for somatostatin, it couldn't be found. The experiment failed. And I recall vividly Bob telling me that his life passed before his eyes, and others informing me that in fact Swanson checked himself into a hospital. Ultimately it was determined that he had indigestion but had taken it for something more serious.

Hughes: Explain the context--why Swanson would be so agitated about the seeming failure of this experimental approach.

Kiley: Well, he was attempting with a small amount of money to do something that hadn't been done before, and while the experiment had a logical premise, it was, as many experiments are, heading into the unknown. Indeed, the worst thing about the unknown is that sometimes you don't know what you don't know--the so-called unknown unknowns or "unk-unks," as I've heard them referred to. And so while one expects the science to work, when it doesn't, one doesn't necessarily know why or what it is about nature that is unknown that needs to be known to make it right.

Hughes: Plus Swanson himself was not a scientist, so it must have been difficult for him to assess what the scientists were determining.

Kiley: I think Bob may have had, for a layman, a pretty good grip on the science as it stood at that time.

Failure and Then Success

Kiley: But he had raised a very modest sum of money. The first infusion from Kleiner and Perkins was $300,000 that came in at least two tranches. I think Genentech began with $100,000. It got another $200,000 when we signed up the City of Hope, and that sum, significantly less than Riggs and Itakura had sought from NIH, was all he had to work with. And he had one shot.

It is common nowadays in ventures to plan, as Bob did then, to take more money after risk is reduced by achieving some financeable benchmark. In fact, Tom Perkins very recently reminded me of one of his key tenets for investment. That is, design an experiment that can establish quickly whether the technology is feasible--fail fast. Well, I think what

Bob saw in the initial somatostatin failure was the proof of that principle. That he had failed, and more money might not be forthcoming.

In the event, the people involved figured out what had gone awry and fixed it. It turns out that while the genius of somatostatin as a choice made for a more convenient synthesis, the DNA being smaller than that for insulin, the resulting product was also small enough to attract the attention of enzymes within the bacterial cell that degraded the expression product before it could be picked up in the assay. The design for expression had somatostatin being expressed with a small piece of an enzyme called beta galactosidase fused to it. It was Riggs who proposed that would be no problem since somatostatin's start signal, ATG, could be cleaved with cyanogen bromide.

Well, in the wake of the initial failure, Riggs said, "Let's just leave a lot more of this superfluous DNA attached to somatostatin, with the idea that it will wrap itself about the target protein and protect it from enzymatic degradation until the conjugate can be gotten out of the cellular environment, then cleaved to yield the end product." And when that was done, Swanson's bellyache went away and he had, as Handler later said, "a scientific triumph of the first order."

Hughes: Do you remember the approximate time interval between the failure and the success?

Kiley: I think there may have been two failures, and so perhaps Bob's bellyache was a persistent one. Aside from the enzymes chewing up the product before it could be seen, there had earlier been some mistakes in synthesis, so that the fragments that were assembled proved not to be correct in their entirety, and that work had to be redone [I may be confusing this with the insulin work]. I think that several months may have passed between the initial mishap and the ultimate achievement.

Resistance to the Commercialization of Academic Biology

Hughes: Do you want to talk about the political and economic environment in which all this was happening in the late 1970s? Cohen and Boyer's basic work on recombinant DNA technology was first published in 1973, and a lot was happening in the basic science. But the somatostatin research, as you say, was really the first proof that the technology had commercial potential. What was there in the national environment that was affecting the growth of commercial biotechnology?

Kiley: Well, remember I said I was oblivious to much that was going on before I met Swanson and began to live it only afterwards. Most times seem like normal times when we're living through them, and it's only by comparison to times later in life that they seem to possess distinctive characteristics. Looking back, it is remarkable that a company could be formed so successfully at a time when entrepreneurialism was on the wane in America, when America was pretty down about itself, when we were emerging from the effects of the Arab oil embargo, still smarting from our losses in Vietnam, at a time when President Carter was complaining of economic malaise, and interest rates were at an all-time high; at a time when no new pharmaceutical company had been formed in the United States since Syntex. Syntex

had had the advantage of pulling itself into existence before the 1962 amendments to the Food and Drug Act greatly raised the bar and made entry into the pharmaceutical business profoundly more difficult. In the midst of this, here is Mr. Swanson proposing to make dollars out of DNA.

Now, recombinant DNA, or as it was unfortunately called then, genetic engineering--with the overtones of eugenics that carries--was very controversial. At Asilomar a few years earlier [1975], a moratorium on conduct of the science had been called for. There was deep concern that Congress would bring its heavy hand to bear on conduct of the science, and perhaps in a meat axe way rather than surgically so. There was great concern about biohazard. People fear what they don't understand, and there was a lot not to understand, from a lay perspective, in what seemed like vast new powers over life--virtual sorcerer's wands in the hands of apprentices. And here in the midst of all this was Swanson with his eye on one goal, and that was to produce human insulin that might be less subject to allergic reactions than animal-derived insulin, that would free diabetics from reliance on animal parts for supplies of their medicine. And Swanson seemed remarkably unflappable about the controversy.

It's more remarkable that Boyer was able to bring himself to partner with Bob and so become a lightning rod for criticism. I recall the *Berkeley Barb* at the time published a stinging attack on Boyer for having gone commercial and accompanied it with a graphic showing the intertwined serpents of the caduceus, but instead of serpents' heads, there were fists grabbing greenbacks. *People Magazine* did an article on Boyer with the then customary references to Frankenstein and so on, somewhat reminiscent of the reference nowadays to so-called "frankenfoods."[1]

Hughes: This bad press was slipping off Swanson's shoulders? He was going ahead regardless?

Kiley: Well, he was. Bob, like many great entrepreneurs, was very single-minded and very goal-oriented, and having set himself in a certain direction, he trudged through whatever was required to attain it. People who devote their minds to more complex subjects often get lost in them. I think one of Bob's great geniuses was his ability to stay the course toward discrete objectives.

What Boyer did was not unusual when seen against the history of industry-university interactions in other sciences. It was highly unusual in molecular biology because, so far as I know, from the time [James] Watson and [Francis] Crick elucidated the double-helical structure of DNA until gene-splicing, no one had figured out how to make any money from DNA.

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Kiley: And they were perforce pure scientists, scientists not bent on commercial application, because the commercial applications of DNA were largely unrecognized until the gene-splicing work was done by Boyer and Cohen.

So here is Boyer who is drawing lightning for two reasons: first, his name was on the Boyer-Cohen patent application [on the recombinant DNA process], that was itself controversial; and now he had gone commercial. Scientists unused to the commercialization of their science and unacquainted with patents generally were evincing concern over divers effects that were expected from this coincidence of issues. How would commercialization

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[1]See appendix.

affect the free exchange of information? How would the patents that are a concomitant of commercialization impede their science? What science would be done in the university under corporate sponsorship? What would be the effect of that--directing science away from basic questions and toward bottom-line commercial applications? Would university science move from the basic toward applied research? Would the free exchange of materials be imperiled, or would postdocs be misused by company principals who were tenured professors? Would companies rushing in where universities feared to go, and doing so with precipitous speed in the minds of academic scientists, evoke Draconian legislative reactions that would in turn determine what science could and couldn't be done at the university level? And here was Boyer, in the eyes of many of his colleagues, going for bucks, in a way and at a time that complicated their lives.

Fear of Biohazard and the NIH Guidelines for Recombinant DNA Research

Hughes: There was also another issue related to patenting as an incentive for commercialization. Scientists worried that the use of recombinant DNA was going to create biohazards. Now you had the threat of this technology being transmitted into industry which would not be under any governmental control; the NIH guidelines [for recombinant DNA research] applied only to government-supported research, not industrial research done with private funding.

Kiley: Well, you're certainly right that patents are incentives to the commercial development of science. I recall that Jeremy Rifkin, the notorious gadfly of biotechnology, in his brief *amicus curiae* to the Supreme Court, when the question was asked in the [*Diamond v. Chakrabarty*] litigation whether patents should issue on new forms of life, took the position that patents should not issue lest practice of the science be encouraged, because practice of the science was dangerous, in Rifkin's untutored view. The more patents, the more practice; the more practice, the more danger.

There came a time when I heard scientists in universities complain that they could be out-competed by their colleagues that had gone into companies because the companies were in some cases better-equipped, because it was easier to create cross-disciplinary collaborations within a company environment than between academic departments; that companies were not obliged to endure the grant application process, and so on and so forth. I don't think that those were concerns of scientists in the formative years of Genentech because, of course, that industry competition was not well developed.

The NIH guidelines were not made applicable to industrial companies, but it was very clear to all of us the cost of violating the guidelines--or not voluntarily complying--would be great. So most companies, in my experience, did their level best to comply with those guidelines; took [for approval regarding biohazards] their proposed projects before the [NIH] Recombinant DNA Advisory Committee, and so on.

Threat of Federal Regulatory Legislation, 1977-1979

Kiley: It is an accident of history that the first projects of Genentech, both somatostatin and insulin, did not fall under the guidelines by their very nature. The guidelines said nothing about expression from synthetic DNA, which perhaps is an unwitting recognition that to do what Genentech did was not so obvious as others might later have claimed. Indeed, not obvious to Paul Berg, witness his remark after the fact that it was "astonishing" that things could be expressed from synthetic DNA. I think [NIH Director] Don Fredrickson did a remarkable job, and more than anyone else, can be credited with fending [off] ill-advised and improvident legislation that might have unduly suppressed benefit [from recombinant DNA technology] out of fear of risk.

Hughes: Explain how he did that.

Kiley: Well, in 1977 Senator [Edward] Kennedy introduced legislation that would have severely regulated practice of recombinant techniques in university and commercial laboratories. The Asilomar conference had been convened with the notion that science should demonstrate it can regulate itself. [Two] years after Asilomar, here comes the Kennedy legislation. But here comes Don Fredrickson and the National Institutes of Health with a host of advisors putting together the guidelines, putting together the compliance programs, and jawboning industry to go along, to the point where Congress could feel comfortable in holding its hand and taking a wait–and-see attitude.

Well, having waited, what have they seen? Twenty-five years later, a cornucopia of benefit from recombinant DNA and no one has caught so much as a case of the sniffles. And so Congress was wise to wait. Fredrickson and the NIH gave them reason to wait--elaborating the self-regulation of science that began with the moratorium and Asilomar. And we're all the beneficiaries of that.

Drawn to Swanson and His Corporate Mission

Kiley: When Bob Swanson approached me, I had very little experience in business transactions as against trial matters. Indeed, the arrangement with City of Hope was the first intellectual property agreement of any kind I'd ever negotiated or drafted. What Swanson wanted to do really wasn't what I was doing at that time, but I was gripped by it. And I liked him. I admired his chutzpah in aiming with this controversial technology to mount barriers to entry that stood high around the pharmaceutical industry; admired his moxie in doing that on what seemed a very small amount of money--so small that I did everything I could to spare him expense: from sleeping on his couch in San Francisco when other clients were putting me up at the Stanford Court or the Fairmont [Hotels], to charging him for the brief I prepared for Genentech in the Supreme Court matter [the *Chakrabarty* case] only what it cost to print it. Genentech was becoming a labor of love, if you will.

Hughes: What was it about Genentech that caught your attention? Or was your attraction mainly focused on Swanson?

Kiley: Swanson was Genentech.

Hughes: Yes, I know that.

Kiley: And I admired him. Boyer was hovering in the academic stratosphere, and only later did I come to know Herb well. But it was the technology junkie thing. I was getting to look over the shoulders of people who were manipulating genes, or as was commonly and redundantly said in the press in those days, "tinkering with life itself," and that was interesting to me.

I must say San Francisco had its own attractions. Ever since the permanent press trial I'd been looking for other excuses to come to San Francisco, and Bob was one even if I had to sleep on his couch. Ultimately when Swanson asked me to leave my partners and to move to San Francisco as a full-time employee and officer of the company, I discussed it with my partners, who said, "It sounds fascinating. We would do it if we were you, and if it doesn't work out, you can always come back home." So I think I may have been the only employee of Genentech who took no risk in joining it. Certainly never regretted having done so.

Hughes: When did you do that?

Kiley: Bob popped the question in October of 1979, and I joined formally on the first of February, 1980. By then I had represented the company for a little more than three and a half years, gotten to know all the employees intimately. It was not as if I was joining strangers, but rather moving from one set of friends to another. By then I was an intimate and trusted confidant of the company, consigliere in some ways. I had participated in the negotiation of the company's arrangements with major pharmaceutical companies having to do with growth hormone and with insulin and with interferon; and written the company's patent applications to that point, its brief in the Supreme Court and the inferior court on the question whether life could be patented; had been involved in the evolution and ultimate settlement of threatened litigation on the part of University of California. So by the time I walked through Genentech's doors as a full-time employee it's fair to say I was hip deep in the company's issues and culture.

Company Policy on Patenting and Publication

Hughes: Had you in the previous years at Lyon and Lyon more and more focused on Genentech as opposed to other cases?

Kiley: Of necessity, although it was episodic because I had other responsibilities. For example, when the key work on human growth hormone cloning was going forward--a matter that later became controversial[1]--I was obliged to take a hiatus from my Genentech work to defend a personal injury claim to a jury in Fresno. I recall coming home from, if I may say so, a splendid win in that case to find that growth hormone had been cloned. I had to scurry

[1]Mr. Kiley alludes to the University of California, Eli Lily, Genentech case involving early work on growth hormone, of which more is discussed below.

up to San Francisco to attend to the patenting of that, because on the fifth of July, 1979, Dave Goeddel intended to reveal all at a conference. On the fourth of July I was busily scribbling away at the patent application so it could be filed before he stood up and spoke, which typically was the way it seems things were done at Genentech.

I recall reading your oral history of Neils Reimers and his assertion that patenting never held up publication at Stanford.[1] Well, no more so did it do at Genentech, in part to keep the scientists happy, and largely because we thought publication was important at Genentech. One of Herb Boyer's great contributions was insisting that Genentech publish its work. It helped us attract scientists who crave the peer recognition publication brings. It acted as quality control, that being one of the great points of refereed journals. If you can pass muster with the referees and get published in a reputable journal, you're doing good science. It helped to validate the company in the eyes of potential customers. If you will, it enhanced our celebrity. And it greatly aided us in recruiting the best and brightest from academic centers, where traditionally they'd been chary of industry because of the perception, not inaccurate, that, in industry and particularly in the pharmaceutical industry, trade secrecy trumped publication.

Hughes: What was the situation in the pharmaceutical industry?

Kiley: Well, it's presumptuous of me, but I'm a presumptuous person: what I observed in my earliest exposures to that industry was that companies tended to be monolithic, tended to practice their science behind closed doors and without any significant degree of inter-company collaboration. There was a modicum of sponsored research at universities, with obligate publication. But even that occurred to a much lesser extent than it does presently because many universities did not regard themselves as free to grant exclusive licenses to company-funded research, hence there wasn't as much company-funded research.

Strategies to Achieve Profitability

Kiley: Genentech proposed, of necessity, to bootstrap itself by partnering with major pharmaceutical companies in order to get the science done without undue dilution through the sale of equity. In part because we didn't have enough equity to sell to pay for all the science that had to be done, the trick would be to partner with others and license to others products and technology to the extent required, while hoping that enough would be left that we could build a company that sold a product for its own account, or in Bob's terms, a real company as distinct from a research boutique.

So out the door went human insulin: not a product we regarded ultimately as one that would fit our hands. Out the door went foreign rights to growth hormone. Out the door went worldwide rights to alpha and beta interferon. And all of those were done for logical reasons. Insulin was as close to being a commodity as could be found in the ethical

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[1]Niels Reimers, "Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents," an oral history conducted in 1997 by Sally Smith Hughes, Ph.D., Regional Oral History Office, The Bancroft Library, University of California, Berkeley, 1998.

pharmaceutical industry. It required a huge sales force to detail general practitioners. Interferon was a potentially powerful substance, but one whose mechanism of action and proper indications were largely unknown. There was a great deal of risk. We thought it wise to ship that off to [Hoffmann- La] Roche. In the growth hormone case, we thought to build our sales capacity first at home, before essaying the hard task of establishing ourselves overseas.

In America we have the fortune to start with the largest marketplace in the world, and that a domestic marketplace, and so we could sell foreign rights to growth hormone and keep American rights with a view toward building our company around that product. At the same time, our partner company, Kabigen, a subsidiary of KabiVitrum of Sweden, was not well established in the United States and so less disposed to insist on worldwide rights, as many larger companies would.

It's remarkable to consider that for, I think, five quarters before Genentech went public--indeed, perhaps for longer than that--it turned a profit. And nowadays of course it's almost considered anathema for a company to be profitable at the time it goes public; it means it hasn't been spending enough to develop basic science. But considering the relative vacuum of new company start-ups--that was characteristic of Genentech's formative years, the fact was that in no wise did we consider until the eleventh hour an IPO [initial public offering]--was a slam dunk. The notion that Bob strongly espoused [was], "Let's show that we, our management, can focus on the bottom line. Let's show that we can run a business."

Hughes: Do you think that was a product of his business school training?

Kiley: I believe he thought, and he persuaded the rest of us, that only profitable companies were public companies or could get through the IPO door. And that at a time when even profitable companies going public were not common. You didn't see a lot of technology-based companies popping out on Wall Street in the wake of the Carter years. Those were hard times by comparison to modern times.

Initial Public Offering, October 1980

Hughes: Were you surprised at how fast the company moved to an IPO?

Kiley: I was. I joined the company full time in February of 1980, and it went public on October 14, 1980, and that was a very near thing. All sort of things could have derailed that.

The *Diamond v. Chakrabarty* Supreme Court Case

Hughes: Such as?

Kiley: Well, I mentioned earlier the *Chakrabarty* matter. The Patent Office, in its wisdom, had decided Congress never intended patents to issue on new forms of life. Its reasons for drawing that conclusion were technical. I won't go into them at length. But basically the Patent Office concluded that since Congress had passed special legislation to protect plant varieties, it must have done so because it perceived the protection of living things was not envisioned by existing patent law and so it had to layer onto existing law protection for plant varieties.

Others took, as we did, the position that the patent laws are written in broad terms, as a broad mandate or charter for innovation of all kinds. The Patent Office didn't buy it, and until that issue could be resolved, they suspended the examination of all patent applications claiming microorganisms or other living beasties, whether genetically engineered or not. That cast somewhat of a pall over the nascent [biotechnology] industry, and raised questions in the minds of potential investors whether the fruits of deep investment and research would be protected.

The matter went from the Patent Office to the Court of Customs and Patent Appeals [which later became the Federal Circuit Court of Appeals] where Genentech participated as a friend of the court. The company basically submitted a so-called *amicus curiae* brief, which I happened to author. The case then went up to the Supreme Court at the behest of the Patent Office. The Court granted *certiorari*, and the outcome was a matter of some concern because in an earlier decision, which I think was called *Parker v. Flook*, the Court had made some offhand comments presaging an adverse result in *Chakrabarty*, unless advocacy and clear thinking ruled the day.

Well, there were many friends of the court in the Chakrabarty matter, almost all of them favoring the grant of such patents. The principal opponent I recall was Mr. [Jeremy] Rifkin and his then front, called the People's Business Commission, which excoriated the notion that patents could issue on new life forms. We persuaded the Court. Indeed, it was Genentech's argument that the Court adopted in ruling that anything made by the hands of man was a fit subject for patent laws, and in particular that nothing in law prevented the grant of patents on new forms of life.

A dissent in the lower court [Court of Customs and Patent Appeals] had said if Congress intended to add so remarkable a thing [as patenting life forms] to the patent laws, it would have said so. Our point was had it intended to <u>subtract</u> so great a swath of science and so much potential for benefit, it would have said so. The dissent below had said that if a whole new area of technology is to be added to patent laws, only Congress has the refined ability to deal in depth with the sociological consequences of that. We stood the argument on its head and told the Supreme Court it was being asked by the Patent Office to legislate in Congress's stead; that if Congress wished to <u>delete</u> from the patent laws this great potential for benefit, only it was constituted to make the sociological judgments involved. We thus gave the Court an excuse to pass the buck on to Congress. It did.

By the time [the issue] got to Congress, the benefits [of biotechnology] were rolling in and one could say to Congress, "This goose is laying some golden eggs here. Don't mess with it." And to their credit, to this day, they haven't. And eggs abound. [tape interruption]

Now had the Court come out the other way, what might have occurred with Genentech's offering? I have no doubt the terrific reception we got on Wall Street when we went public was amped up by the publicity that attended the Supreme Court's ruling just the preceding June saying that our products could be patented. Had it gone the other way, I'm confident it would have cast a pall over investment. Whatever the technical merits of the decision, the emotional impact would have been, to investors not disposed to inquire more deeply, that we could spend a lot of money developing new science and not own anything in the end result; and that would make fund raising very, very difficult. So had the Court gone the other way, I think we would have been significantly wounded.

Regents of the University of California v. Hoffmann-La Roche, Inc. and Genentech, Inc.

Kiley: There was another matter. One of the last achievements of the company before it registered for its offering was cloning the various alpha interferons. Interferons then were hot subjects and bruited about in the lay press as potential cures for cancer and so on. We had done that work in collaboration with Roche. We had a consultant by the name of David Golde. He was sitting in my office one day up from the University of California at Los Angeles. And David said to me, "Tom, I see from your alpha interferon publication that the messenger RNA you used to clone the DNA came from a cell line called KG1. Do you know what KG stands for?" "No, David, I don't." "Tom, it stands for Koeffler-Golde. That was my cell line and Genentech used it without my permission. What do you think should be done about that?" I said, "Well, I think we will look into that, David."

It developed Dr. Golde had obtained this cell line from a patient, had provided it to Dr. [Robert] Gallo at the National Cancer Institute, who later became controversial in respect to isolation of the HIV virus. Gallo had passed either a culture of the cells or a messenger RNA from it to his friend Sidney Pestka at the Roche Institute, who in turn passed it on to Genentech where it arrived bearing no indicia of ownership, at a time when people were not disposed by nature to dig into the provenance of tangible biological materials. David Goeddel and others at Genentech succeeded in cloning alpha interferon from messenger [RNA] obtained from these cells.

Well, there is a whole body of law in personal property law that follows tangible things into constructs, and it deals with the rights in ownership that result from that. Someone steals my timber, fashions it into lumber, which is then worked into your barn. Now according to the law, I have an ownership right in your barn. Likewise, UCLA claimed and the Regents [of the University of California] claimed they had ownership rights in our alpha interferon product. We were in registration for our IPO; the University of California sued Genentech and Roche, and the general counsel of the University of California permitted himself to say to the press, which reported it in large black font, that Genentech had perpetrated a "billion dollar gene scam" against the tax payers of California.

Well, these are not circumstances in which one expects a good reception on Wall Street. I called Ellis Anderson who was senior vice president, general counsel of Roche, our collaborator, and I said, "Ellis, this lawsuit comes at an awkward time for us." "Yes," he

said, "it's terrible. I'm sorry." I said, "Ellis, we would like you to indemnify us against any money damages." "Why should I do that," he said. "For good will," I said. "All right, all right," he avuncularly agreed.

I then approached Lyon and Lyon and asked them if it wasn't right that in a matter so affecting the public health and welfare if we were found to have done anything wrong, the court would impose only money damages and no injunction against bringing this potential cancer cure to the patients, and the firm provided an opinion to that effect. We were now able to say in our prospectus that the suit in any circumstance would leave us unmarked: no money damages--Roche would take of that--no injunction, no harm, no foul.

Hughes: Did investors buy that?

Kiley: Well, witness the success of our offering.

Hughes: Yes, share price rose from $35 to $89 in the first few minutes of trading.

Kiley: The lawsuit played no effect. It ultimately was settled without the payment by Genentech of a single cent. [tape interruption]

Peter Seeburg, Axel Ullrich, and Allegations of Stolen Cell Lines

Hughes: Anything else that might have derailed the public offering?

Kiley: Well, there was, now you mention it, another contretemps that got resolved at least insofar as it could be, and that was with the University of California as well.

Genentech in 1978 hired, from the University of California at San Francisco, two scientists, Peter Seeburg and Axel Ullrich. They were among the foremost workers exploiting so-called cDNA [complementary DNA] technology which is gotten from RNA by what is called reverse transcription. As we moved from somatostatin through insulin toward larger proteins like human growth hormone and the interferons, it became apparent that DNA synthesis would increasingly be impractical, given the crude state of its then development, as the proteins got bigger. And so we needed to add expertise in cDNA cloning in which we let the enzymes and the bugs do our synthesis for us. Peter in the growth hormone field and Axel in the insulin field had been advancing that technology.

After they were hired, I was called to Genentech to hear their tale of woe. It developed they had carried away from the university some biological material, tissues and clones, they had--

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Kiley: --used in work that was ongoing. Having no experience other than university experience, they were distraught at the notion they would be unable to complete for publication manuscripts about the work they had done at the university, some of which needed to be

cleaned up in the laboratory. But when the laboratories [at UCSF] in which they had worked learned of their intention to join Genentech, a perceived competitor in both the insulin and growth hormone areas, the walls had come down.

These scientists had removed their materials thinking that only by doing so could they complete academic aspects of their work and get publication credit. The university was now calling for the return of those materials. Letters that grew increasingly heated were coming from Roger Ditzel, the contracts and grants administrator at the university. He was at Berkeley but had become responsible for systemwide intellectual property management [at the University of California].

Our principal interest at this point was to placate these young scientists because we regarded them as important additions. They were distrustful by nature of industry and all that connoted. Here, the very first time they ventured into industry, what had resulted was a storm of recrimination and accusation, threats to their reputations, and the possibility that they would not receive publication credit for their work. And they said patent applications had been filed by the university on their work, in which they had not been credited as inventors.

Well, we sought to placate the university by first treating this as if the university issue was over transfer of recombinant materials unaccompanied by the memorandum of understanding spoken of in the [NIH] guidelines. We offered such a memorandum with retroactive effect. "No," said the university, they wanted the materials back, and every bit of them. And this went on for quite some time.

I then obtained declarations from Dr. Seeburg and particularly from Dr. [John] Shine who had left the same laboratories and gone to Australia carrying many of the same materials with the blessing of those who ran the laboratory. Dr. Shine expressed the view he had done so in complete accordance with custom and usage in the field of molecular biology, that these materials were common currency and commonly went with departing scientists, as did their laboratory notebooks and so on.

Legal Counsel for the University

Kiley: Well, the controversy subsided for a time and then it heated up when the university engaged a fire-breathing old war-horse by the name of Ed Irons, who was the sort of a fellow who while a complete professional, gives lawyers a bad name the way brain cancer gives cancer a bad name--just mister tough guy. Ed is always looking for a reason to pull the trigger, and suddenly he saw us looming in his gun sights and thought, "Ah, ha!"

Hughes: How did he become aware of the case?

Kiley: [sigh] I'm not sure what attracted Roger [to Irons] other than perhaps the perception that the lawyer with whom he began was not getting him anywhere. There was a fellow by the name of Lorance Greenlee who was doing technical work for UCSF who was another of these fellows that combined a law degree with a graduate degree in life sciences. I think that

Greenlee may have become an associate of Irons's firm, and Irons stepped in and turned up the temperature.

Well, I had the opportunity to read the University of California's brief submitted in the *Chakrabarty* matter, and I was surprised to find in that four pages of vituperative attack on Judge Charles Rich of the Court of Customs and Patent Appeals. Rich is a revered figure in patent law, who largely authored the 1952 patent act (Title 35, U.S.C.), and here was this pro hominem against Rich in a brief in the Supreme Court. I called Mr. Ditzel and I said, "Roger, I'm surprised to find this in your brief. Don't you know that the University of California will on frequent occasion find itself before this court, and what is the point of so personal an attack on a revered judge?"

He was shocked to find that was in the brief. He later told me that he had reviewed the draft of the brief before it went to the printers and that was not there, and had been added afterwards by Mr. Irons, who within a matter of hours was disengaged by the University of California and was no longer a thorn in my side. [laughs]

Then came to the fore Bert Rowland. Bert was the author of the Boyer-Cohen patent and, from a Patent Office standpoint, a very accomplished lawyer. He took pride in the fact that he had never stood up in a courtroom in his life. He was, as he put it, "A lover and not a fighter, and a settler and not a litigator," and, "Couldn't we make a deal?"

Genentech Settles with the University of California

Kiley: We were coming up on the thirtieth of June, 1980, and any controversy that lived beyond that time would of necessity be carried as a contingent liability in the registration document we proposed to file in connection with our IPO. It became mandatory that we settle this matter and eliminate that overhang before the thirtieth of June, 1980.

Hughes: That was the cutoff date beyond which the suit had to be mentioned in the IPO prospectus?

Kiley: From an accounting perspective.

And so we settled. We agreed to pay the University of California $350,000 and change, and a modest royalty on growth hormone sales until the royalty payments exceeded five million dollars, with adjustment for inflation. And in return, the university released us from any claims that might have arisen from our possession of any tangible biological materials or any use that may have been made of them, and at the same time was unable to grant us a pass under any patents that might emerge from the work that the university had done in connection with those materials.

Well, we said, we understood that. That work was funded by Eli Lilly; Eli Lilly has an option to take an exclusive under those patent rights, therefore, you're not in a position to grant us any rights. But we're not concerned about that because we were the ones who cloned the human growth hormone; we won the race.

And so we left unsettled the issues of patents. We took some comfort in the fact we had won the race, and it should follow in logic that we would have the patents and they would not. And on the thirtieth of June, 1980, we disposed of all other aspects of the case and got away in the prospectus with a footnote to the effect that we'd settled a dispute with the university of California in return for the payment of $350,000, etc.

Hughes: A sum like that is arrived at by negotiation between the parties?

Kiley: It's a negotiation. In my view, we owed them nothing. In their view, we owed them a great deal. And we came out with a sum that was enough of a difference to make Mr. Ditzel's year look good--more than pay for his legal expenditures. I think that most of that money was distributed. I believe the university settled for the royalty and distributed lump sums to Drs. [William] Rutter and Howard Goodman and John Baxter who were the loudest voices complaining about the Seeburg-Ullrich matter. In fact, I was told at one time that they each went out and bought Porsches with their money. So how was that sum arrived at? It was, I think, a number big enough to get Rutter, Baxter, and Goodman off of Roger Ditzel's back. Interestingly, in the footnote [prospectus] disclosure for settlement, we were able to offset it against $300,000 that had been paid us to settle another controversy, and so it became a wash. That money came in settlement of a claim that Bob Swanson asserted against Biogen.

International Nickel

Kiley: Inco--International Nickel--had either invested early in Genentech, or had looked closely at Genentech in connection with a potential investment, and then had gone off to become one of the principal backers of Biogen. Swanson took the view in his discussions with the Inco people that his whole modus operandi and business plan had been exported to Biogen after having been revealed in confidence to the Inco people. In order to placate him, they said, "Look, why don't you just go on the board of directors of Biogen?" And so they called a meeting, I think somewhere in France, and it was one of their earlier formation meetings, and Swanson showed up--to the horror of all others concerned. "What's he doing here?" The Inco guy said, "Well, I proposed that he join our board. Let him sit in the lobby while we debate this." So Swanson cooled his heels for several hours in the lobby and then they came out and sent him packing and he persisted in his complaints, no longer placated by the offer of a board seat. Ultimately, to buy peace, someone wrote him a check for $300,000. And just by coincidence and no more than that, we were able to align these in the prospectus, so it all reduced to sound and fury signifying nothing.

We will revisit the Seeburg-Ullrich controversy because, while we settled enough to get public, it heated up later when, against all the odds and improvidently, the Patent Office granted a patent that purported to cover recombinant growth hormone, on the strength of animal and incomplete human work that happened at UC San Francisco while they were losing the race to Genentech. And that patent asserted years later gave the university an opportunity to pull from its briefcase the bloody shirt of the Seeburg-Ullrich matter and it disposed a jury of San Francisco people largely against the company--about which more later. [laughs]

IV GENENTECH

[Interview 2: September 22, 2000] ##

Swanson's Initial Vision of Genentech

Hughes: Mr. Kiley, what were your impressions of Bob Swanson when you first met him?

Kiley: Well, the first impression he made on me was that of a very young man for what he proposed to do. He had longish hair, as was the style in the seventies, albeit receding in front--as mine subsequently did. He was a small man, albeit stocky. I remember *Esquire* magazine saying once of Bob that he's not a very big man unless he's standing on his wallet. That was after the public offering. [laughter] Very outgoing, very positive in his approach to what he saw as a great business opportunity. Not the sort of fellow to take no for an answer. And warm and witty, which led to our fast friendship, as well as the business relationship we had over many years.

Hughes: Were you convinced by his arguments?

Kiley: He said he was going to form a major independent pharmaceutical company and, while typical of my profession I embraced the opportunity to charge him for my time, inwardly I have to say I was skeptical. I think the thought was something like, "Sure, you are, kid." In the event, I didn't charge him very much for my time, so things worked out within his means.

At that time I had little experience with the pharmaceutical industry. I didn't realize how forbidding a prospect it was to propose to form a new pharmaceutical company. I had no idea of the many years required for clinical testing. And starting from scratch, that meant many years of effort without any sales revenue to bolster R&D [research and development] expenditures. Had I known that, I think I would have been even more skeptical of Bob's prospects for success.

Hughes: Why do you suppose he started with that rather grandiose plan, rather than of aiming to be, as I assume most small start-up companies in science are, an R&D contract institution?

Kiley: Well, remember Bob had just come from employment at Kleiner and Perkins, and Kleiner and Perkins was a venture capital group. Venture capitalists can return funds to their limited partners only if they can take a company public or sell a company to a public company so that

they have liquidity. And if Bob was going to take venture capital, which was required, and coming from a venture capital perspective, he had obviously to build a for-profit company so that his own investment of time and energy could result in a liquid asset.

I think Bob may have also taken on what Tom Perkins regards as among the critical tenets of venture capital investment: where is there an opportunity that has a major marketplace, that has technology with multiple applications, and where the technology risk can be assessed and reduced with a relatively modest upfront investment? What Bob proposed to do fit all that. The pharmaceutical industry is a profitable industry. Everyone sooner or later turns to it in time of need. The gene-splicing technology, though early in its lifetime, plainly was a powerful technology capable of widespread application--someday. And how far off that day was could be determined by seeing if one couldn't trick a bacterium into making a human polypeptide, and Bob reckoned correctly that that could be done with a reasonable sum of money. He was right.

Early Applications of Recombinant DNA Technology

Hughes: Did you ever hear of any early consideration of applying the technology to a field other than the pharmaceutical?

Kiley: There was a time when people referred to four companies as constituting the big four of biotechnology: Cetus, Biogen, Genentech, and a company on the East Coast called Genex. Genex proposed industrial applications of the technology, that is, not agriculture, not animal health care, not human health care, but the production of chemical substances.

Genentech itself for a time pursued those opportunities in addition to the health care opportunities that became its mainstay. We looked, for example, very hard at producing the amino acid constituents of Aspartame (TM) and had extensive discussions with the folks at Searle on that account.

We had a joint venture with Prutec of England to investigate the possibility of producing rubber in bacteria. And indeed, we sent people to South America to smuggle home samples of tissue from the rubber tree, from which we proposed to extract [RNA] message, clone the various enzymes used in the production of latex, and then envisioned tanks filled with bacteria that would secrete latex which would float to the surface and be skimmed off. It turns out that biochemistry of rubber production is a little more complicated than we thought at the outset. Nothing came of that project.

Focus on Pharmaceuticals

Kiley: In respect of other so-called industrial applications, we concluded we were competing with economics that had been refined over the last century. People who make fine chemicals and synthetics of various kinds are using organic chemistry principles that have been elaborated over the course of many, many years, and they've squeezed an awful lot of cost out of the

process. Our conclusion was it wasn't clear we could add significant value there on a broad front. And of course the other thing that drove us to focus was limited resources for the very substantial investments required for pharmaceutical development, and our need to put our scarce dollars where they would give us the biggest bang for the buck.

Hughes: I'm thinking of Boyer, who even before he met Swanson, was thinking about the commercial potential of the technology. It would seem that Boyer's orientation certainly was for medical, pharmaceutical application; he was a scientist in a medical school.

Kiley: Well, not only in a medical school, but in a school that at the time may have been the second largest recipient of federal dollars for medical research.

Technological Risk-Benefit Ratio

Kiley The other nice thing about focus on the pharmaceutical industry is that when, as happened in the seventies, this nascent industry was confronted with critics who voiced great concern over potential biohazard, we could enlist the support of various patient groups. Everyone knows someone who's got a bad disease, and there is something called a risk-benefit ratio. While people were stacking on one of the risk scales all these imagined concerns about biohazard, we could stack on the other balance pan all the potential boons that might result. And that I think leads governing officials to look at things with some balance.

Hughes: You made a point in one of your papers addressed to an attorney group that if the potential for biohazard arising from recombinant work is accepted, it would be indefensible to practice the science without taking steps to insure that benefits accrued.[1]

Kiley: Well, you may be referring to notions I've expressed over time that impediments to commercial practice would not prevent academicians from pursuing the science. Commercial practitioners were more likely than academicians to invest in containment, given corporate liability. And there's very little difference, when you're talking about a microorganism, between an academic scientist with a petri dish full of them and a manufacturer with a ten thousand liter tank full of them, because the bacteria in the petri dish can grow exponentially and if released and if they proved hardy enough to survive in a non-laboratory environment, could quickly rival in scope any industrial spill. So if the genie was out of the bottle, and if indeed there was the potential for harm, there was also the potential for benefit, and we might as well take the good with the bad.

Hughes: Well, I think your argument was even stronger than that: If we're going to practice this technology at all, then there is an obligation and a responsibility to see that benefit accrues from it," meaning products of use to society. It was an argument used in the contention over the Cohen-Boyer patent.

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[1]Thomas D. Kiley, "Patent and Political Shock Waves of the Biological Explosion," reprinted from the *Proceedings of the Southwestern Legal Foundation Patent Law 17th Annual*, 1979: 253-85, 275.

Kiley: Well, I may be repeating myself, but Abraham Lincoln said that, "The patent system added the fuel of interest to the fire of genius." When the issue of patenting the Boyer-Cohen technology was being debated in academic circles, the point was made patents were necessary if the kind of investments required to take academic science and develop it into commercially practicable form was to be encouraged. In the event, the Boyer-Cohen patent was licensed nonexclusively rather than exclusively, so the argument breaks down. More commonly one hears that argument as a justification for the grant of exclusive licenses to patents arising from government-funded research, where in order to get benefit, you need what Lincoln called the "fuel of interest." And that means patents, that means exclusive rights to protect the fruits of investment. And so in the Bayh-Dole Act, the government granted to universities the right to exclusively license federally funded inventions.

Hughes: What role did you and Genentech play in the congressional debate of the mid-to-late 1970s about possible legislation to regulate all kinds of recombinant DNA research, industrial as well as academic?

Congressional Testimony

Kiley: I'm not sure that Genentech's voice was heard above the din in those early days, considering that the company had, in 1977 when Senator Kennedy's bill was introduced, only a single full-time employee and very little money. In the latter seventies and early eighties, the company testified through various of its representatives. I did so to both houses at the California legislature and to various [federal] congressional and Senate committees.

I remember a time when we were seeking some amendment to the patent laws that was opposed by the usual opponents to the pharmaceutical industry--the Association for Retired Persons and so on. The argument was made that the industry was greatly overblowing its potential. "It was doubted," said one opponent to the legislation we sought, "whether as many as 2,000 jobs would be created by biotechnology." I said in reply that, "Genentech itself would create 2,000 by the end of the decade if not sooner," and indeed we did. [tape interruption]

Locating Genentech in South San Francisco

Hughes: Where was Genentech originally located?

Kiley: Actually what that brings to mind is how Genentech came to build its operations in South San Francisco. The politics of the time were such one could anticipate controversy wherever one located a gene-splicing laboratory. Indeed, people were marching in Berkeley chanting "We shall not be cloned." Bob Swanson was driving up Highway 101 one day and he looked up and saw emblazoned on Mt. San Bruno the legend, "South San Francisco, the Industrial City," and decided that might be a less controversial place to house his new company. Genentech at that time had been in operation for several years, basically operating out of a rented office at Kleiner and Perkins.

Bob got on the phone with the city fathers of South San Francisco, told them what he proposed to do, and as he reported it to me, they could have cared less so long as, quote, "You don't dump any drugs down the sewer," end quote. Genentech thereupon rented 9,000 square feet in a freight forwarding warehouse at 460 Point San Bruno Boulevard--now known as One DNA Way, by a recent proclamation of the city--and for the first time had its own facility.

The facility then contained three offices, a reception area, three laboratory rooms, and before long, a 60-liter fermentation system, which we could never quite get to work. Next door was a warehouse that held stag films between rentals. When they came back, they had to be hand-cranked through a viewer to make sure they were fit, if I may use that term loosely, to be rented out again. There was a hole in the wall between our fermentation room--then under construction--and the blue movie theater or warehouse, and we found that scientists were looking over the shoulder of the fellow while munching their sandwiches during their lunch break.

Ultimately Genentech moved down the building. It is not true that we encouraged other tenants to give up their leases by making bad smells and hypothecating release of deadly organisms. Nevertheless, before long, we occupied the whole of our first building. Lord knows how many biotech companies have followed Genentech into South San Francisco, but I think it may be the densest concentration of such companies anywhere in the country. I proposed once in a talk to the Chamber of Commerce in South San Francisco that it rename itself the Biological City, and I think that could be done without making it impossible for people in advance of the [University of California-Stanford football] Big Game to go up and paint their school colors on various of the letters on the hill.

Early Business Plans

Hughes: Do you have a comment about the earliest business plans that you glanced at before we began recording?[1]

Kiley: The first plan that I saw proposed to potential investors, I think, a 77 percent internal rate of return on bulk sales of insulin to pharmaceutical companies. On the basis of that product alone Swanson could forecast an appropriate return.

Hughes: Was it the insulin that caught potential investors' attention?

Kiley: I'd have to speculate. I never asked, for example, Tom Perkins, what caught his attention. It was not lost on Bob and Herb that there would be applications other than insulin for so powerful a technology. But Bob's business training came through, and rather than take to the venture capitalists a "Gee whiz, Mister Wizard" sort of tome on the promise of the technology, he had a fairly well-worked-out financial forecast, providing a concrete example of how the technology could be applied--in real time, to a real product; a product essentially like one

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[1]For example, "Outline for Discussion: Crocker Capital," March 12, 1976; "Genentech, Inc., Business Plan," December, 1976 (both documents in Chief Financial Officer files, Genentech).

already approved for human administration--with a reasonable investment of capital. And venture capitalists respond to that sort of businesslike approach.

Early Diffuse Corporate Focus

Hughes: Indeed, I would say a theme of those early documents is that Genentech proposed to focus on two or three products for which there was a readily obtainable market and also a system in place for marketing them.

Kiley: Well, I wish I could say that Genentech was focused from the start. That history is a little different. Bob before long had arrangements with Merieux Laboratories in Paris to do work on the hepatitis front. We had an arrangement with International Minerals and Chemicals to do a foot and mouth disease vaccine. We had an arrangement with Chemi Grunenthal of Germany to do a product called urokinase. We had arranged with Roche a collaboration in the interferon field. All these in addition to growth hormone, insulin, and so on. And we were looking at animal health care applications and beginning to look at industrial applications, all before the initial public offering in 1980.

In fact, having got a number of these projects going, some came to the fore in part because we experienced success in the laboratory, and in part because we were obliged to concentrate resources on a limited number of discrete projects if any of them were to get anywhere. There did come a time when Genentech made the conscious decision to exit the animal health care area, to exit industrial applications more or less. It did the latter by spinning off as opportunities into joint ventures of various kinds.

Hughes: Why was that?

Kiley: Well, there were several reasons. I've mentioned the resource constraint. There's also a cultural constraint. The pharmaceutical industry is fundamentally different from agribusiness. One is very, very price sensitive; the economics of chicken production are incredibly difficult to alter. So you would have to have separate sales forces that had different philosophies about serving their markets. Agricultural applications involved shipping tons and truckloads of material as against 50-milligram vials, and so on. So in the end, Genentech made the courageous decision to go after the most profitable sector [laughter] and sold off its assets in other fields.

I remember when we decided to exit animal health care, Mark Hirsch [V.P. business development] and I were sent out on the road, and we happened to knock on the doors at Ciba-Geigy just after its board of directors had directed management to get back into the animal health care business, from which I gather antitrust concerns had excluded it after Ciba and Geigy merged. But that was fortuitous timing and we wound up turning essentially all of our animal health projects over to Ciba-Geigy for forty-two much needed millions of dollars and a carried interest.

Hughes: Well, you've just described the diverse fields in which Genentech was working prior to the IPO. It was also a time when the scientific force at Genentech was small. How did you find scientists to spread around on all these projects?

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Kiley: [The somatostatin project] was carried out at City of Hope and the University of California. The insulin project also benefited from City of Hope lab input and could be taken on because David Goeddel and Dennis Kleid had joined us as among the company's first molecular biologists. Indeed, it wasn't until laboratory success was had with insulin that Goeddel was able then to turn to human growth hormone. The other projects I mentioned above as having got going prior to 1980 of course had the benefit of a larger staff. By the time we went public in 1980 we may have had on the order of 100 employees. The great majority of them were scientists.

Hughes: Who were devoted to one project? An organic chemist, for example, would work exclusively on one project rather than dancing from one to another?

Kiley: Well, it depends upon the discipline. Molecular biologists tend to concentrate on a discrete number of projects, focusing on one--two or three at the most--in, say, the case of the interferons. On the other hand, other disciplines operated for a long time in somewhat of a service capacity. So, for example, DNA synthesis would take orders for probes and coding constructs of various kinds and ship them out to particular molecular biologists. The same was true with [culture] media preparation and so on, as is typical in any biotechnology company.

Negotiating Research Agreements

Hughes: What about the contracts and patents that went along with some of these projects? You must have been the instigator.

Kiley: I don't think I was the instigator. I was, if you will, the facilitator. The first agreements with the company were negotiated by Bob Swanson and myself--the City of Hope arrangement, the University of California arrangement, the Kabi arrangement on human growth hormone, and the Eli Lilly arrangement on insulin. And before very long, he brought in marketing people. The first was Bob Byrnes, who came from American Hospital. Others followed in Bob's wake, in particular, Jim Gower, also from American Hospital. Jim is now the CEO of Rigel Pharmaceuticals. Gary Steele headed up the industrial applications marketing. A fellow by the name of Jim Leith came from the Elanco division of Lilly to head animal health care.

Typically what happened in business development was I or a member of my staff on the law side would team with one of the people from marketing and do the negotiations in a sort of a tag team fashion where we exchanged the good-guy, bad-guy hat faster than the other side could keep up. [laughter]

Hughes: Genentech had no marketing capacity when you were doing the somatostatin work, or the insulin, right?

Kiley: That's correct.

Hughes: Well, recreate one of those negotiations.

Kiley: Well, a negotiation is a courtship, and in my opinion it begins with establishing your credibility, finding out what your prospective partner needs, persuading your prospective partner that you can supply its needs, and making an assessment of how valuable that supply is to your partner so that you can price your services appropriately. So any negotiation involves a series of meetings in which people first get acquainted and then sort of go through a funneling process that leads them, hopefully, to converge on agreement.

Hughes: The tenor is business rather than science?

Kiley: Well, certainly it's necessary if you're selling science capability to satisfy science-competent people on the other side that you can do what you propose to do.

Hughes: Was that left to you, or did you have a scientist in tow?

Kiley: Oh, we would produce the scientists at the appropriate time. But I've always felt that you're best off talking first to the business side of a company. Because what we thought we were offering were strategic alternatives to major pharmaceutical companies, and companies like that are willing to spend, perhaps beyond their budget--certainly beyond the R&D budget--to grasp an opportunity they perceive as strategic. On the other hand, if you're making your pitch to research people, they're operating within the confines of given R&D dollars in their budget, and in effect, as an outside researcher, you're competing with them for those funds. Well, it's much easier to go in over the research group and capture the attention of someone who's rewarded in the organization for building sales, irrespective of where the technology comes from.

So in our discussions, we invariably found ourselves talking to the highest officials in companies. It wasn't always easy to get to see them until Genentech obtained some celebrity, but Bob Swanson, bless his heart, would find a way in the door.

Recombinant Human Insulin

The Contract with Eli Lilly

Hughes: Lilly, as a major manufacturer of insulin, was naturally interested in human insulin. But was the Genentech contract also a test case for the technology as far as Lilly was concerned, maybe even thinking they would want to develop recombinant DNA capability in house?

Kiley: Certainly insulin was important to Lilly. It was a product around which the company had largely defined itself through much of its history. It was the dominant supplier of insulin in the United States. I think it was generally right that, in the 1970s in particular, so-called genetic engineering was very hot from the standpoint of controversy. There was a natural reluctance

on the part of large companies who had customer constituencies to be seen as involving themselves directly in what some thought was a dangerous technology. So it was politic for them to farm out those sorts of activities.

Hughes: It was really that, you think? Not, "We're not sure about this technology. We don't want to make an investment in it until it's proven. We'll just let this upstart company take the risk with it."

Kiley: No, I don't think that's right. In the case of Lilly in particular, Dr. Irving Johnson, who held a very high seat in Lilly's research establishment, from the beginning understood that biotechnology would be big. Indeed, he led Lilly more than any other pharmaceutical company in the early days to redefine itself around biotechnology.

But when we first met the Lilly people, they didn't have anyone in-house who had significant competence in the new technology. We did. The University of California did. We were both determined to work on insulin, and I think Lilly must have concluded that if they competed with us, they would get beaten, and having decided they couldn't lick us, joined us in one sense. In fact, Lilly was funding an insulin effort at the University of California, thought the UC workers would beat Genentech to insulin, and entered an arrangement with Genentech simply to hedge their bet. So it backed both horses in the race, if you will.

The Gilbert and UCSF Insulin Projects

Hughes: Was that known to you at the time?

Kiley: I don't think so. At least it wasn't known to me. It may have been known to Dr. Boyer. They did not back the third horse, which was Wally Gilbert at Harvard University.

Hughes: I wonder why.

Kiley: I don't know. In fact, perhaps they did and I'm not aware of it.

Hughes: I've never read that.

Kiley: I'm sure that *Invisible Frontiers* contains the answer.[1]

Hughes: No, I don't think there was a contract between Lilly and the Gilbert group.

Kiley: I recall with some amusement Dr. Gilbert's plaintive musings about having lost the race. He had adopted an approach that required a P4 level of containment. On the very day when we were announcing success in insulin, he was, as he had for many days past, trudging through an airlock, dipping his shoes in formaldehyde on his way into the chamber in which he was

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[1]Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene*, Redmond, WA: Tempus Books, 1987.

obliged to conduct his experiments. While out at Genentech we were simply synthesizing DNA and throwing it into bacteria, none of which even required compliance with the NIH guidelines, although we always endeavored to work in compliance with those guidelines.

Hughes: Remember, in relation to human insulin, a UCSF group retired to France, ostensibly to escape the purview of the recombinant DNA guidelines.

Kiley: I think this is right, and I think Axel Ullrich would confirm that. The key experiments had been done outside the guidelines at UCSF and were subsequently repeated in France in an effort to obscure the guideline violation. I think Steven Hall may recount that as well in his book.

More on the Somatostatin Project

Contract with the University of California

Hughes: In the case of somatostatin, one of the contracts was with the Regents of the University of California.[1] Was that to the university a standard sponsored research agreement, nothing more, nothing less?

Kiley: I don't know a lot about the history of the University of California in sponsored research agreements at times prior to 1976. Certainly the UC-Genentech agreement looks fairly plain vanilla when viewed by current standards--in contrast, I may add, to the City of Hope agreement. The City of Hope agreement gave Genentech title to any inventions that arose in the course of the funded work, in return for a royalty only on drug products whose DNA had been synthesized at City of Hope. The University of California agreement, on the other hand, consistent with university policy, said that the university would retain title to any inventions its employees made in the funded work and that Genentech would have an exclusive license under those patents so long as it paid a royalty when it sold products covered by the patents. The agreement also provided that the university would get an additional royalty without regard to patents for what it called "know-how received."

Now, I didn't like that language. I didn't see it until the agreement was signed. I think Bob, in an effort to achieve some economy, did a cut-and-paste job on the City of Hope agreement and, in the ultimate negotiation of final terms, agreed to pay for this know-how. I had a problem with that because it's very difficult to govern know-how in a collaboration of that kind: what know-how has been transferred, what projects has it touched, what are your obligations under it? Ultimately, in the course of another negotiation, we cleaned that up.

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[1]Sponsored Research Agreement, August 1, 1976, University of California Office of Technology Transfer, 77-064-1, folder: Goodman, et al., Rutter, et al., Deposit of Microorganisms [sic].

Disagreement over Inventorship

Kiley: The reason I mention the difference in the two agreements as regards inventorship is that when the somatostatin work was done, it fell to me to determine whether inventions had been made and if so by whom. I concluded that a number of patents should be filed--initially four applications for patent were filed--and that no University of California worker was an inventor. Josephine Opalka was the patent administrator at that time, and she had a lot of problems with that. Certainly the University of California people had made contributions to the work in the form of ligating various DNA fragments together, and so on.

Hughes: That would have been [Herbert] Heyneker and [Francisco] Bolivar?

Kiley: And others in Boyer's laboratory, yes. Ms. Opalka's view, simply expressed, was since Boyer was a leader in the field, he must have been at least a co-inventor in the somatostatin project. My rejoinder was that I could find no evidence of an inventive contribution on Boyer's part; that because he had been granted a patent for his pioneering work in gene-splicing, it did not follow that he was an inventor of every application of gene-splicing.

For years afterwards, the university railed about that inventorship decision. I think from their perspective it seemed too convenient that only City of Hope inventors would be named, so that Genentech would own outright the patents and the university would receive only modest royalty for know-how in defined categories. Over and over we made available laboratory notebooks and other evidence supporting our attribution of inventorship, and ultimately the university, if not satisfied, at least stopped complaining about it.

Hughes: It's a bit ironic, it occurs to me, because the Cohen-Boyer patent was being prosecuted around this time. Two of the co-authors on the UCSF side claimed that they should be named as inventors on the patent application because their names were on the scientific publications. But the determination by the patent attorney was that they were not inventors. As you know, Cohen and Boyer remained the sole inventors on the patent.

Kiley: Well, deciding who invented something is not free from difficulty. It falls into the metaphysical category of perplexing issues that Justice Felix Frankfurter said abound in patent law. And because the determination of inventorship looks largely to the conceptual element as against physical labor, workers are often unhappy to find that the person over whose head the light bulb went off gets, quote, "all the credit," where they at his or her instruction labored long in the laboratory to reduce his conception to practice--or her conception. But that's the way the law works.

It is quite unlike the process one goes through to determine authorship for purpose of scientific publication. Indeed, I remember sitting through one long day, keeping my mouth very shut as the authorship of the somatostatin paper was debated amongst City of Hope and UC San Francisco workers. I learned from that never to assume that all authors on a paper are of necessity inventors on a patent. [There is] much more politics involved in authorship determination. Everyone whose hands touched the project is listed, as is appropriate.

Hughes: There's an understanding in science about what the first author and last author positions entail.

Kiley: I think it's fought over quite as much if not more than investment bankers fight for position on tombstones that are published after financings.

Early Patents

Hughes: Were those four somatostatin patent applications successful?

Kiley: Many patents grew from those beginnings. Of the four ideas that I saw as potentially patentable coming out of the somatostatin work, three proved patentable to the satisfaction of the United States Patent Office. Then various wrinkles and variations of those three ideas have since appeared in the form of other patents.

Hughes: And what were they?

Kiley: Well, I first decided that despite the prior work of Boyer and Cohen, this was the first time that anyone had ever expressed a foreign protein under what I called "friendly" control. Said another way, the control mechanisms for expression of the foreign DNA were endogenous to the particular bacterial species--or as I called it, homologous control. So we first claimed as a Genentech invention any expression of heterologous DNA under homologous control in a microbe.

Next, Art Riggs had used a trick to save somatostatin from enzymatic degradation when it was expressed. It was, in effect, buried in a larger piece of conjugated protein--in this case, much of the enzyme beta galactosidase. And so we filed a patent claim that purported to cover the expression of any polypeptide in conjunction with superfluous protein which could be specifically cleaved away later to free the desired substance.

Finally, Keiichi Itakura at City of Hope had used the degeneracy of the genetic code to choose codons for particular amino acids according to his view of which codons were preferred for microbial expression. His belief was human polypeptides made in the body are expressed from codons somewhat different from those best suited for microbial expression. And so we claimed as an invention the expression of mammalian polypeptides from codons, the majority of which were preferred for microbial expression.

So all three of these patent applications were examples of taking a specific experiment and, for patent purposes, expanding it to its logical limits so as to cover things in addition to the work actually done--a prominent and maddening practice of patent attorneys. Whether it's right or wrong, it ultimately can become a matter of controversy. The notion is that the breadth of patent protection you receive should be commensurate with the boon you confer on the public by having made your invention. So you can claim anything proceeding from your experiment that can be gotten using your idea without undue experimentation. It doesn't mean that people applying your invention to new objects are spared work; it's just that they're not required to exercise the inventive faculty to achieve a reasonable number of objects.

Hughes: Being first in a new field gave Genentech an advantage, did it not?

Kiley: Well, it certainly gave us something to talk about when we called on various corporations, seeking funding for our work--the notion that we could confer some measure of patent protection, that we had patent rights in train which might ultimately preclude them from dealing with others.

Patents in Early Biotechnology

Role in Corporate Financing

Hughes: What was the status of patenting in the new field of biotechnology?

Kiley: Well, let me say first that patents count a lot more in the pharmaceutical industry than they do in, say, information technology where products are rapidly obsolesced and the patents seldom if ever catch up. In the pharmaceutical industry, on the other hand, products have long lifetimes and so patents can be important in preserving exclusivity. The patents are needed because of the deep investment this heavily regulated industry requires of its participants. Nobody's going to spend hundreds of millions of dollars to get a drug approved if the generics can then replicate the drug and put it on the market in the next month. So I think it was well understood in the earliest days of biotechnology that insofar as pharmaceutical applications and pharmaceutical investment was concerned, you had better have a patent story.

You have to deal with two things when you're seeking finance: logic and emotion. There was a perfectly good logical story that said we'd have all the patent protection we needed, whether or not patents were permitted on the microbes themselves, because within the microbial engine is, if you will, a carburetor that helps it cough into life. That's the plasmid. The plasmid was an absolutely dead bench chemical which could be patented without reference to the controversy over "living" inventions. So regardless of--

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Kiley: --the issue, one could say to potential investors, here is a logical approach to ensuring that our products are protected.

More on the *Chakrabarty* Decision

Kiley: When the court in *Chakrabarty* said you could patent the microbes themselves, why, that was a famous decision--famous because it intrigued the public, amazed the public--patents on new life forms! And so it turned a spotlight on the industry. The decision was regarded as positive for the industry and undoubtedly was a boon to the public offering. Had the case gone the other way, one supposes the emotional reaction would have been very negative, and it might have made it quite difficult for Genentech to go out and for others to follow.

We could convince people that we had a patent story--conviction being a product of the mind--but until the *Chakrabarty* decision we couldn't persuade them that we had a patent story--persuasion being a matter of the heart. Well, after *Chakrabarty* we had heart and mind covered and could get on with our business. [tape interruption]

More on Genentech's Initial Public Offering

Hughes: Tell me how *Chakrabarty* related in time to Genentech's IPO.

Kiley: The court decided the matter in June of 1980 by a five-to-four decision. The IPO was in preparation and took place October 14, 1980, just months later.

Hughes: Could you tell me the context of the IPO?

Kiley: I mentioned earlier 1976 was not a particularly propitious time for offering securities--a risky startup with no products in hand. I mentioned that Bob believed it was important we be able to show successive quarters of profitability before the IPO. We never anticipated the IPO would be received as it was and attended by a remarkable run-up in the stock price and some celebrity. I suppose there was some sign of that. I recall an article, and I think it was in *Business Week*, some weeks before the IPO at a time when we were in a so-called quiet period. The periodical nevertheless headlined its article, "Waiting for Genentech."

Certainly on the roadshow, which I did not attend, we were oversubscribed by a very significant margin. Indeed, the night before the offering, the investment bankers told us we could price the shares at any level we wished and assured us that we would close ten dollars over the offering price. In the event, we had forecast a range of thirty to thirty-two dollars for the shares. We set the price at thirty-five.

Hughes: On what basis?

Kiley: Well, at that time it was somewhat unusual to price outside the range. We thought we could get away with it. Bob strongly believed that we should leave money on the table in the sense the shares should close higher than the offering price so that we would make money for initial investors in the IPO. So I think [he] exercised some real restraint in pricing given the great anticipation that emerged in the immediate advent of the offering.

Several people told us afterwards that we should sue our underwriters for underpricing it. I think the underwriters gave us good counsel. I think Bob made the right decision. The best evidence of that is, while the shares went as high as the eighties--they may have closed at something on the order of twice the offering price--some months later we were actually under water. The shares fell to twenty-eight, however briefly. I think the company was appropriately priced.

I remember Peter Farley, who was an officer of Cetus, had in the weeks prior to the offering said some unhelpful things that were reported in Dan Dorfman's financial column to the effect Cetus did not believe Wall Street understood biotechnology; Cetus wished us luck, but didn't

think a public offering was the right way to go. Ironically, we left so much unsatisfied demand that within months after our IPO, Cetus went out and raised $120 million in their very own public offering, proving that foolish consistency is the hobgoblin of small minds.

Hughes: [laughs] I read that it was the largest ever run-up of stock price on Wall Street--at the time, of course. Is that accurate?

Kiley: I don't know. I certainly heard that said in those days. Of course, the run-up pales by comparison to recent events in the dot com business and related information technologies. But for its time it was a remarkable offering. Afterwards we went to Japan where the *Nihon Shinbun*--I think was the paper--called Swanson "The man who caught the rainbow."

Hughes: The rainbow meant what?

Kiley: The rainbow meant overnight wealth for himself and many others at Genentech.

Hughes: What went into the sudden surge of investor interest in biotechnology?

Kiley: Gene-splicing had clearly captured the public imagination. It was controversial in some of its parts and rather awe-inspiring in others. By the time of its offering, Genentech had forged commercial relationships with Kabi of Sweden, Lilly, and Hoffmann-La Roche for interferon.

The Interferons

Kiley: Interferon was a very hot subject at that time. In fact, *Time* magazine heralded the IF or "if" cure for cancer on its cover shortly before our offering. Many hoped, some believed, that interferon would become a panacea for cancer, and of course interferon was the subject of our arrangement with Hoffmann-La Roche.

By the time of the offering, we had cloned the whole family of alpha interferons and beta interferons as well. Gamma interferon would follow in a few years. I have to believe the interferon craze contributed substantially to the success of our offering. It's ironic for many years after that, interferon was a product looking for an application. Indeed, the first application for which it was approved on Genentech's part was for treatment of hairy cell leukemia, a very rare disease. More recently the interferons have proven of substantial utility in the treatment of hepatitis and multiple sclerosis.

Hughes: But the interferons have never lived up to the hype about a cure for cancer and viral diseases to the extent that was initially anticipated, have they?

Kiley: I think that's a fair statement. There is renewed interest and excitement over gamma interferon in the hands of Intermune Pharmaceuticals which is exploring its utility in the treatment of pulmonary disease. Indeed, Intermune licensed interferon gamma from Connetics Corporation, of which I am a director, which in turn licensed it from Genentech.

Recombinant Human Growth Hormone

The Cloning Race

Hughes: Is there more to be said about hGH?

Kiley: Volumes could be written on that subject. The fact is recombinant human growth hormone was like recombinant insulin--a horse race. The University of California once again was a contender. Lilly was financing UCSF work aimed at growth hormone. We had in the meantime licensed foreign rights to growth hormone prospectively to Kabi of Sweden, and proposed upon cloning it to make and sell it for our own account in the United States.

We had hired Peter Seeburg from the University of California in part because of his expertise in cDNA cloning, which we thought would be the preferred route to growth hormone, given that the molecule is much larger than human insulin and in those days less accessible in practice by the synthetic DNA route. As Peter subsequently testified, he was in a rather distraught state during the early years of his Genentech employment and largely proved unable to carry the project forward.

Hughes: Was his state apparent to you and others at the time?

Kiley: I attributed his distress to the accusations that had been made by his former colleagues at the University of California when he brought some of his research materials with him to Genentech. Peter subsequently admitted to having undergone a siege of substance abuse. Whatever the case, Peter didn't seem to be able to make a start on the growth hormone project.

I had told Peter that I wished him to make no use of the University-of-California-originating materials in his commercial work at Genentech, although it was my understanding that he would make some use of genomic DNA in completing academic work for publication.

Hughes: What motivated you to say that?

Kiley: Well, at that time we were receiving letters from the University of California, taking exception to their having removed their research materials to the Genentech employment. As it happened, I was not yet an employee at the company and was obliged to go off and try a jury case in Fresno. In my absence, Dave Goeddel stepped forward--having completed the insulin work--and took charge of the growth hormone project, and he and Heyneker subsequently succeeded in cloning growth hormone itself.[1] And I emphasize "itself" because they used a technique I referred to in subsequent patent applications as a quasi-synthetic approach that permitted one to tailor the gene so that human growth hormone would be expressed free of any precursor protein.

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[1][Press release], Genentech, Inc., "First Bacterial Production of Human Growth Hormone Announced," [n.d. but July 11, 1979], Corporate Communications, Genentech.

I conclude Goeddel was unaware of my injunction to Seeburg to make no use of the university-originating materials, and I believe subsequent investigations showed that he made cDNA libraries from divers sources, one of which happened to be some of Peter's university-originating material. The evidence at a subsequent trial persuaded me and persuaded many that the actual Genentech growth hormone clone was obtained from a source other than the university material.

Hughes: Do you know what the source was?

Kiley: As I sit here, I don't, but the actual notebooks are available on Genentech's Website.

Patent Rights

Kiley: In the run-up to the IPO we had settled as much of the Seeburg-Ullrich controversy as we could, that is, all issues relating to the tangible biological materials, know-how, and so on. But we did not receive from the university any rights in any patents that might eventuate from Seeburg's work. I said that we felt fairly comfortable with that because we believed, and it is the case, that we had won the race to make human growth hormone. An objective observer would conclude that patents emanating from the University of California shouldn't prove problematic. We couldn't gain access to those patents because they were subject to an Eli Lilly option at the time.

Well, what eventuated was the university succeeded in cloning growth hormone with extra protein attached to it, so did not make growth hormone itself.[1] They nevertheless managed to get a patent claim on the extra protein growth hormone conjugate. And the growth hormone Genentech made was not that; it was that shorn of the extra bit that the university workers evidently did not know how to cleave away.

***University of California v. Genentech*, 1999**

Kiley: Now, there is in patent law something called the "Doctrine of Equivalents." It says you may infringe a patent by activities not literally within the words of the patent claim if those activities fall within some penumbra around the claim, if a court of equity thinks cynical and unfair avoidance of the patent would otherwise result, having in mind the limitations of language in burgeoning new fields. And the university with its patent on this growth hormone look-alike sued Genentech, alleging that Genentech infringed not literally but by equivalents.

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[1]Joseph A. Martial, Robert A. Halliwell, John D. Baxter, and Howard M. Goodman, "Human Growth Hormone: Complementary DNA Cloning and Expression in Bacteria," *Science* 205 (1979): 602-7.

In ordinary course, it would not be permissible to bring to the attention of the jury any of the history relating to Seeburg's having brought university-originating materials with him to Genentech. However, the Supreme Court in the meantime had decided a case in which they defined permissible subjects of inquiry when making a determination whether something infringed by equivalents. One of the elements, the Supreme Court said, was, "copying," the work of another. The university seized on this and managed to persuade Judge [Charles] Legge use of university-originating materials, if it could be proven, would be tantamount to copying the work of the university and therefore evidence probative of infringement by equivalents.

After years of the usual discovery hassle, the matter went to trial here in San Francisco. Using this recent Supreme Court decision, the university was able to shoehorn into the case references to Peter having, if you will, "absconded" from the university with tax-payer property. So now you have a jury of San Francisco tax-payers deliberating a controversy between a tax-payer-supported institution on the one hand and by now a big rich corporation on the other. And the jury hung.

All members but one were persuaded that the claims were infringed. I gather from after-action reports, all members of the jury were persuaded that Dr. Goeddel had done what in fact he did not do, and that is derive the growth hormone from the university-originating material. One juror declined to find for infringement because he concluded, despite use of the material, Genentech's activity did not meet the test for infringement by equivalents.

So Genentech, faced with necessity to re-try the case and with university claims I regard as outrageous, but claims nevertheless they were damaged in the amount of $1 billion, decided as a matter of discretion to settle the case. And it was settled for the payment of some $200 million dollars. I regard the whole affair as the gravest form of injustice. Basically the people who lost the race went to the committee room and claimed the prize, and by an appeal to passion and prejudice very nearly persuaded the jury to give it to them. Genentech's reasons for settling the matter and putting it behind them I can only conclude resulted from their concern whether in the circumstances any San Francisco jury would be expected to do better the next time around.

Hughes: What damages did the university maintain had occurred?

Kiley: The patent laws provide two approaches to a calculation for damages for patent infringements. One is lost profits, which were not applicable in this case.

Hughes: Because?

Kiley: Because they weren't in the business of making and selling growth hormone. Although arguably they might have claimed lost royalty income. But that becomes speculative. Would Lilly have licensed? Would Lilly have paid so on and so forth? The alternative is a so-called "reasonable" royalty. And the university position, I gather, was Genentech had made all of this money, and in the circumstances a reasonable royalty would be on the order of $200 million, which is some reasonable percentage of Genentech's gross revenues, without regard to all of the investment Genentech had made in developing, manufacturing, marketing the product. Who knows what jurors will do in circumstances like that, when they can enjoy vicariously handing out money to an institution of higher learning, playing "Queen for a Day," if you will.

Hughes: You think that was definitely a factor?

Kiley: Well, all trials are morality plays in the end, and it's very difficult to predict with mathematical precision what a jury will do. I actually believe very strongly in the jury system. The collective wisdom of twelve minds is almost invariably better than the conclusions a single judge might draw. I don't regard the outcome of the Genentech-UC matter as just or deserved, but on the other hand, it's over and everyone can get on with their lives.

It's ironic to me Peter Seeburg, who came to me distraught, strongly asserting his entitlements to the use of this material and who in subsequent depositions testified favorably to Genentech's cause, at trial changed his story, admitted that he had answered untruthfully in deposition and supported the university's position in the matter; having earlier won from the university an undertaking to share up to 10 percent of any award given against Genentech. But that's a matter for Peter's conscience.

Hughes: Why do you believe that material from UCSF was not used in the Genentech growth hormone work?

Kiley: I did not attend the trial and can rely only on what's been said to me concerning that by, amongst other things, trial counsel. All that information is readable on Genentech's Website and was the subject of expert testimony in the trial, which the first jury chose not to believe--if they understood it at all, which is always the question.

Hughes: The case is very complicated to begin with, and then you have the science in addition. It would be a real test of communication skill.

Kiley: Well, that's why trial lawyers sidestep the complexity by finding a hook they think will make the jury's job easier: "If the glove doesn't fit, you must acquit." Something as simple as that. Having not attended the trial, I really can't judge the quality of the evidence or the jury's ability to follow it. It's really a matter of deciphering laboratory notebooks which, in this case, amount to a very careful record of the experimentation and the source of the clone.

Hughes: Is that true of Genentech's notebooks from the start?

Kiley: Insofar as I am aware, yes. In fact, I believe the university was obliged to take the position that Goeddel made false entries in his notebook because the notebooks are consistent with Genentech's story. This of a man who is probably the most truthful person I've ever met, is a member of the National Academy of Sciences, one of the very few to have risen to those ranks from an industrial rather than academic base, and one of the finest men I've ever known.

A Settlement with UC, 1980

Hughes: You mentioned a cash payment to UCSF in the early eighties concerning this case.

Kiley: In effect, Genentech settled two matters in the run-up to the IPO. One was the non-patent aspects of the Seeburg-Ullrich transfer of materials to Genentech. The other was eliminating

the uncertainty that I referred to earlier arising from the 1976 agreement under which Genentech was to pay the university 1 percent royalty on something undefined in respect of "know-how transferred"--whatever that was, and without regard to patents–as a condition of settlement.

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Kiley: I insisted we obtain clarity and certainty in respect to this know-how. We confined it to specific products for a specific time until a specific sum had been paid. And indeed, that was worth $350,000 to me in its own right and more, so I was happy to settle on those terms. But as I said earlier, we were obliged, by Lilly's option with the university, to leave a tail on this controversy which ultimately proved to have a stinger in it.

Genentech's Corporate Evolution

More on Swanson's Initial Vision

Hughes: You mentioned at the outset of this interview that you had some doubts upon your first encounter with Swanson whether he really was going to be able to pull off his plan for Genentech. As time went on, did these doubts disappear? Or was there up until the time of the IPO a slight hesitation in your thinking about whether Genentech was going to live up to his expectations?

Kiley: My doubts on initially meeting Bob were probably largely a function of my youth and my felt sense that all important things were done by older people. I don't think I had had much experience with people as young as Bob or myself pulling off anything like this.

Hughes: Were you about his age? He was twenty-eight?

Kiley: He was twenty-eight, and I guess I was thirty-three. I only half understood the science and really couldn't judge whether it was ready to go. Even Bob, when the somatostatin experiment first seemed to have failed and he saw his life pass before his eyes, had doubts whether the science would be pulled off. Once somatostatin succeeded, I think we were all relatively confident that insulin could be made and that we had at least a shot at growth hormone. I don't believe anyone could have foreseen in those days, or did foresee, the vast and multifarious applications to which recombinant DNA would later be put.

From the time we did insulin, Genentech increasingly was in the limelight. People there were hailed as wunderkinds, and I think that we all, after breathing that smoke, began to blow a little of our own and breathe that too; and probably were more optimistic than we should have been, rather than less. I don't think anyone at Genentech in the early years took on a deep understanding of how many hurdles stand between a startup and the pharmaceutical marketplace.

Hoffmann-La Roche Gains Controlling Interest

Kiley: Ultimately, Genentech failed in a certain sense in its drive to become a fully independent pharmaceutical company, or "FIPCO" as was the common term then, in part because the products of its research were greater in number than the means available to take them through clinical development. So it became necessary to tie up with a major pharmaceutical company, in this case Roche which won control of Genentech, in order to have the means to fully exercise the research muscle of the company.

And I think that's worked very well. Genentech today has probably got the deepest pipeline of any of the original biotechnology companies. Remarkably, Roche had the prescience at having acquired all of Genentech to spin out a significant percentage of its shares to the public, so in the end giving Genentech a measure of independence--it is a separately listed company--and at the same time, having removed the lid on share appreciation, let the stock ride up and rewarded the employees who had hung in. And now Roche has the best of all worlds: it owns a controlling interest in Genentech, at the same time it has happy, well-motivated employees, many of whom date from the earliest days of the company.

Hughes: Do you think that Roche's decision was in part due to some appreciation of the necessity of maintaining a culture that had proved to be productive?

Kiley: I can only speculate. I haven't discussed this with anyone at Roche and indeed not with anyone currently in management at Genentech. It's plain Genentech was acquired by Roche for its existing product revenue, but also for its core scientific competency. As people used to say, "The greatest assets of Genentech go home every day in their tennis shoes." So keeping [the scientists] happy is a way of keeping the company productive. And I think Roche has succeeded in doing that.

Hughes: Considering the differences drawn between the culture of a pharmaceutical house and that of a biotech company, it seems to me a no-brainer that Roche should leave Genentech essentially alone.

Kiley: The people at Roche are very smart. The culture of a Swiss-based pharmaceutical company is very different from that of a Silicon Valley biotechnology company. Both sides take the science with deadly seriousness, but California-based companies don't take themselves quite so seriously as in my experience do the Swiss. But because the Roche people are very smart, they're fully capable of accepting cultural differences while tuning the company for optimal performance.

Hughes: So you think that they have the best of both worlds?

Kiley: In Genentech they've got a very precious asset. I don't know if life at Genentech today is quite as zany as it used to be, and that may be simply a function of the people having grown up, having had families, and it may also be a function of its being a publicly owned company. Certainly there was nothing Swiss about the Friday night bashes that Genentech inaugurated.

Ho-hos

Hughes: Tell me some of the anecdotes about the Ho-hos.

Kiley: I attended Genentech's first Ho-ho in, I think, 1978 when I found, in the sole conference room at five o'clock on a Friday, Bob sitting with three or four scientists, a paper plate with salami and bread on it, and a six-pack of beer. From that acorn a mighty oak grew. [laughter]

The Ho-ho's became competitive. One would sign up to sponsor a Ho-ho and design it. And so, typical of molecular biology would be the Junk Food Ho-ho in which nothing healthy could be served but Twinkies abounded. Another of the molecular biologists, Ron Hitzeman, threw the Colonel Sanders Ho-ho at which fried chicken was served and chocolate and custard and other pies. And the notion was, "The Colonel loves the pies that fly," so these of course became pie fights--which upset Bob no end.

I remember Dave Goeddel, wearing a plastic face shield used when you're dealing with corrosive chemicals, running across the cafeteria with a pie in hand; someone coming up behind him and flipping up his face shield and pushing the pie he held in his own hand square into his face. In fact, when I left Genentech, I took to my retirement ceremony a tuxedo, imagining if I wore a tuxedo no one would dare hit me with pies. Of course it was like waving a red flag in front of a bull. I remember a Hawaiian Ho-ho that Swanson intended to be civilized, so roast pig, and various people came and did hula dancing. In the midst of it, those fun guys from molecular biology released a half a dozen greased pigs into the crowd and a greased pig chase ensued. [laughter]

David Martin, who was vice president for research at that time, claimed that he was going to restore civility to the Friday afternoon bashes, and so the following week announced a Ho-ho with a French theme and that champagne would be served. Since the theme was French, he had brought from Calaveras County a dozen jumping frogs, each of whom had a little necklace with a nameplate of one member of the board of directors around it, and betting ensued on a frog race. So it went.

I recall chasing Desiré Collen (from whom we licensed certain aspects of tissue plasminogen activator), a revered professor in Belgium, down the parking lot with a lemon meringue pie in my hand, nailed him squarely in the head. He'd never seen anything quite like that at the University of Leuven.

Hughes: Was Swanson serious about trying to establish some decorum?

Kiley: I think he blew hot and cold on it, frankly. When the right monkeys lived and the right monkeys died in an experiment involving interferon, Swanson and I declared the Combined Simian Memorial and Revival Ho-ho to which we wore gorilla outfits. I recall being in line at the cash register with Bob when we were shopping for the Ho-ho--bananas, peanuts, things of that nature--telling him that we had forgotten the paper plates, to which he replied, "Monkeys--don't--need--plates." [laughs]

Hughes: Sounds to me as though you entered into the spirit pretty willingly.

Kiley: Well, it is true that water fights often accompanied the pie fights at the Colonel Sanders Ho-hos, and there was an occasion where every employee walking past the reception desk on the morning of the Friday Ho-ho got a water pistol which I'd had brought over from Galoob Toys in South San Francisco. I'm not sure how much work got done in the run-up to the ensuing Ho-ho.

I remember Mark Jackson, not content with a water gun, loading up a big plastic carboy with dry ice and water, mounting it on his back, with a piece of surgical tubing to spray the pressurized contents at various people. Unfortunately, his stoichiometric calculations were not all they should have been, and as he was coming down the stairs into the cafeteria, his carboy exploded, driving the plastic shards into the walls like grenade fragments. It was fortunate that he wasn't in a crowd at the time.

Hughes: Did the Ho-hos continue as long as you remained at Genentech?

Kiley: Yes. They afforded an opportunity for any member of the company to talk informally with any other member of the company. At some point I think that concerns about alcohol arose and the parties had to become much more civilized to avoid liability.

Practices did evolve at the company over time. I know before the public offerings, scientists used to pitch pennies in the hallway. After the IPO, Dave Goeddel invented something called "Bowling for Dollars" in which, instead of pitching pennies, you'd roll up a dollar bill into a tight little wad and see how close you could roll it to the wall. I'm afraid the whole biotechnology industry has got a lot more sober in recent years. Perhaps that's to the good, considering its high mission.

Hughes: Well, some of it had to do, don't you think, with the youth of the people involved initially, and the fact that it was a small, tightly knit group.

Kiley: Well, I think that play is important. And one sees it throughout the valley these days in foosball facilities and gymnasiums--one thing or another. Even the Japanese have their versions in terms of the evening drink-a-thons in the Ginza District that give an opportunity to heal the wounds of shared life-long employment and the frictions that can arise. As I say, it still goes on, to some extent.

I know that the Ho-hos were replicated in companies that were later formed. For example, GenenCor, an industrial enzyme company we formed with Corning [Glass], called its Friday parties Zyme Time. Geron, of which I'm a director, has a Friday night party referred to as the "Geronimo," and so it goes. I think what has diminished the Friday night bashes more than anything else is that people have married, had children, have families to go home to, and for that reason are less inclined to stick around after hours. It's still the case you can differentiate a mature company from a rapidly growing company by counting the cars in the parking lot after hours and on the weekends.

Genentech Work Ethic

Hughes: And initially there were a lot of cars in the parking lot at Genentech after hours, were there not? Wasn't it a many, many hour-a-day operation?

Kiley: It was. People were motivated; they were competitive. They were racing their colleagues around the world toward similar objects. I think that Dave Goeddel was a big part of that. He's got an incredible work ethic. He cloned alpha interferon at the end of a year of 100-hour weeks, and then turned around and did another such year for gamma interferon. When you've got somebody setting that kind of a standard, then people will follow. He does it to this day as CEO at Tularik.

More on Kiley's Decision to Join Genentech

[Interview 3: December 11, 2000] ##

Hughes: We talked earlier about your joining Genentech full time. Why did you decide to do that, and what risks and advantages did you foresee?

Kiley: I've already said by the time I joined Genentech I was hip deep in its affairs and its culture, and so it was not a matter of leaving my good friends at Lyon and Lyon to join strangers; rather, I was going from one set of friends to another and continuing in a more effective and efficient way the interesting things that I'd been able to do with Genentech while at Lyon and Lyon. I've also mentioned that my partners left the door open for my return if it didn't work out, and so I was one of the very few, if not the only person that joined Genentech in the early days that could do so risk free.

I had tried my jury cases, had argued my cases in the courts of appeal, and had taken depositions, examined witnesses on the stand and so on, and here was an opportunity to expand my horizons by learning more about how business is conducted, to become a member of a multidisciplinary group, and to learn from others. A trial lawyer is very much like a solo performer, whereas in the context of a company an individual operates more as a member of an orchestra. Lawyers tend to be somewhat one dimensional: they take bites out of factual situations as they pass by, but they don't make facts for themselves. They live around lawyers and are judged by lawyers. Company employment gives you an opportunity to be in a richer milieu, involving yourself with people from other disciplines, all converging on the solution of complex problems. It seemed like an interesting next thing for me to do, and so it proved to be.

Hughes: What did your colleagues think about your decision?

Kiley: They said it sounded fascinating; they'd do it if they were me, and if it didn't work out, of course I could come back. I expect there was also a certain amount of unhappiness. In the whole history of the law firm, proceeding from the first decade of the twentieth century, only one partner had left it, other than through death, and that was one of the Lyon brothers who had a family disagreement. So I became, with that exception, the first partner to leave the firm

other than through retirement or death. I have to say that several have since followed my example and joined the biotechnology industry as well.

Hughes: Can you think back to what you thought were the prospects for Genentech?

Kiley: Well, by the time Bob asked me to join full time, we had cloned insulin and somatostatin and growth hormone, and the interferons were in the offing. We had established relationships with Lilly and Kabi and Roche, and so it was pretty clear the company had legs. We had raised significant sums of money from private sources. I don't think I anticipated when I joined the company the initial public offering would come within a year. It surprised me and some others in the company when the window opened and that became possible.

I will confess to having some concern whether there would be enough at Genentech to keep me busy because the company was working on a discrete number of projects. There was, with one exception, no litigation in the offing. The Supreme Court brief [in *Diamond v. Chakrabarty*] had been completed and filed. What would there be for me to do? And I guess the short answer was, to work with marketing folks in corporate partnering efforts, and so on. It wasn't clear to me that would fully occupy my attention. But in the event, I was happily surprised. There proved to be more work than even I could do, and I hadn't been at Genentech very long before I was hiring lawyers to help me.

Kiley's Association with Hybritech

Hughes: You had had a stint a few years before that with Hybritech. What was that about?

Kiley: Brook Byers [of Kleiner, Perkins, Caufield, and Byers] asked me to get involved in Hybritech shortly following its formation in 1978. That struck me as the other branch of the biotechnology revolution--gene-splicing on the one hand, in the Genentech case, and hybridomas and monoclonal antibodies on the other in the Hybritech case. Hybritech proved to be the first monoclonal antibody company. And so I met at Brooks's suggestion with Ivor Royston and his colleague Howard Birndorf. Ivor Royston has gone on to become a venture capitalist in his own right, while continuing his researches. Howard Birndorf has been the founder of many companies in addition to his co-founding role at Hybritech.

Frankly, my involvement at Hybritech was largely confined to straightening out some issues of ownership of proprietary rights between the University of California and the Veterans Administration, which employed Ivor Royston. Then the company seemed to chug along rather well, without the need for legal intervention, until the time came when I was obliged to drop them as a client and move on to Genentech on a full-time basis. I left Hybritech in the hands of my then partner, Larry Respess, at Lyon and Lyon, who subsequently became vice president and general counsel, first of Hybritech, then of GenProbe, and ultimately of Ligand Pharmaceuticals, where he currently resides.

Kiley's Early Concerns at Genentech

Hughes: Circa 1980, how were you applying in biotechnology the package of experience and knowledge that you had about intellectual property law?

Kiley: Well, at my initial employment in 1976, there was nothing concrete to apply, given that the somatostatin work hadn't yet been done, and so my interest was in the question of whether organisms would be patentable. I became the chairman of a special committee of the Patent, Trademark and Copyright Section of the American Bar Association to look into the patentability of microorganisms, and indeed got three resolutions passed supporting that notion at the annual meeting. I also got involved in monitoring and, to very modest extent, debating the question what legislation should Congress adopt, if any, to regulate the biotechnology enterprise. That dealt more with biohazard than with intellectual property issues.

Genentech and the Cohen-Boyer Patent

Kiley: I was obliged to look hard at the Boyer-Cohen patent, which promised to interdict Genentech's own efforts unless we could obtain rights under it. At that time, Stanford was evolving its ultimate policy of licensing that patent on a nonexclusive basis, and so the question simply became, on what terms would those licenses be available and would they be economically practical?

Hughes: Were those licensing terms a considerable concern to you and Swanson?

Kiley: I think [they were] until it became clear that the Stanford approach would be to adopt a royalty rate below the threshold of irritation in the industry with a view toward getting the greatest possible number of licensees under the patent.

The other issue there was the extent to which the university would charge higher rates to companies that created systems and licensed them to third parties who in turn would take to market the products those systems produced. And indeed Stanford did adopt the approach of asking for a higher royalty where it was the means of producing a product rather than an end-product itself that became the royalty base. In the event, all that proved relatively manageable, and indeed many of Genentech's own licensees themselves had taken licenses from Stanford, so they took up the royalty burden themselves rather than having it added to Genentech's.

Hughes: Do you care to speculate on the development of the industry had Bob been successful in his original quest to get exclusive license rights to Cohen-Boyer?

Kiley: Well, that would be speculation indeed, because one question that's got to be asked is whether the Boyer-Cohen patent would be upheld in all of its breadth if put to a litigation test. In the event, it was not put to a litigation test because, first, the royalties were made sufficiently low so people chose to license rather than litigate; secondly, because there were few companies willing to be seen as attacking the university's entitlement to a royalty where it was clear that a signal contribution had been made.

One of the features of the pharmaceutical industry that governs all pharmaceutical companies is the question, how many products can any given company push through the clinical development pipeline? Imagine that Genentech owned, as we once sought, exclusive rights to all mammalian polypeptides made using the Boyer-Cohen technique. Well, that would be an elephant-sized body of rights, but how to push that through the keyhole of the FDA regulatory process? No company could raise funds sufficient to develop all the products of biotechnology through the marketplace, and so Genentech would have wound up substituting itself for Stanford as a licensor to all comers for areas outside its immediate focus on particular drugs or indications.

It would have been very difficult for Genentech to attack the Boyer-Cohen patent itself, given that a Genentech founder was named as an inventor of it. And that was certainly a consideration that was before us.

The Status of Patents in Biotechnology

Hughes: I understand that there was some question whether biotech patents would actually stand up to litigation; biotech patents were an unknown quantity. Yet intellectual property was from the very start considered at the core of this industry.

Kiley: Intellectual property is at the core of any heavily regulated industry, at least one whose regulations require the expenditure of hundreds of millions to get products approved. Because you can't justify that expenditure unless you can amortize the expenditure over a long product lifetime, and that implies the ability to exclude others from riding your coat tails into the marketplace. I would say people fear what they don't understand, and it was certainly fashionable in the early seventies for investors to say they didn't understand biotechnology.

I think patent attorneys were more comfortable than the general public or the investing institutions with the notion that there would be sufficient patent protection, whether or not patents were granted on living things. So there would be patents on plasmids, patents on other absolutely dead bench chemicals that needed to be used if things were to be made in microorganisms. But say the patent attorneys were comfortable, it doesn't follow the investing institutions or general public would dig deeply enough into patent law to figure that out for themselves. To them, either you can patent the new microorganism or you can't, and if you can't that's a problem for biotechnology. And so it was a matter of atmospherics as much as the niceties of the patent law that was of concern.

Hughes: Did you have any concerns that patent applications and the patents themselves would be treated any differently than patents in other fields?

Kiley: I do recall that Marshall Dann, who was then the commissioner of patents, first purported to expedite the examination of patent applications in biotechnology, perceiving them to be important; and subsequently, when issues were raised over the patentability of the subject matter, halted the examination of all biotech or microorganism-claiming patents pending the resolution of that question by the Congress or the courts. And so there was a period when there was, if you will, a moratorium on the examination of these applications until matters could be

settled. Plainly it was an issue, and had we not conceived it to be an issue, I don't think we--meaning Genentech--would have participated in briefing the issue, both in the intermediate court and the Supreme Court.

More on *Diamond v. Chakrabarty*

Hughes: Was it obvious to anybody interested in the *Chakrabarty* case that the decision would have an impact on the development of commercial biotechnology, or was it the *amicus* briefs that made the connection?

Kiley: Let's remember what the particular patent application was about in that case. Chakrabarty had, or purported to have, cobbled together a microorganism that would digest oil slicks and so clean up the ocean. There were organisms of various kinds that had developed appetites for particular components of crude petroleum. He gathered together the bits from various organisms that ate various components of crude petroleum and stuffed them all into one bacterium. So now he had a bacterium, so it was said, with appetite for many of the components. It didn't involve gene-splicing as such.

The fact gene-splicing had in the meantime burst upon the scene certainly turned up the heat on that issue. It would be very difficult for the courts to say living things of one kind could be patented, but not another. So had the Court gone the other way on the [patenting of] non-recombinant organisms and plants before it, clearly there would have been a spillover effect into recombinant organism claims. Indeed, that point is nowhere better illustrated than in the fact that while the *Chakrabarty* court claimed to be deciding the matter only with respect to microorganisms, and it disclaimed any view of the question whether higher organisms could be or should be patented, patenting such organisms is now commonplace. Witness the oncomouse of Harvard University, patents on the various farm animals that carry human genes for the production of human products, and so on.

Hughes: Well, my understanding is that while *Chakrabarty* opened the door, it didn't make it a clear entry for patenting these later higher organisms that you've referred to.

Kiley: The [Court] said that it had abiding conviction that the patent laws contemplated the patenting of anything made by the hands of man. So it certainly left the door open a sufficient crack to push a whole Noah's Ark of animals through. That's ultimately what happened.

Hughes: The Supreme Court, as we are seeing so graphically as we speak in connection with the Gore-Bush debacle, is certainly not immune from social pressure. Do you think that in the case of *Chakrabarty*, what was now very clearly a promising industry at a time when the country was worried about innovation and competition could have shaped the decision?

Kiley: Well, Mr. Dooley said, "The Supreme Court listens to the election returns." There grew up a practice, for which Justice Brandeis got credit when he was an advocate before the Supreme Court, of filing what are called Brandeis briefs. These bring to the court's attention matters outside the written record of which they can take judicial notice to put, if you will, a penumbra of the human condition around the dry legal proposition a party may have brought to the court.

The justices of the Supreme Court are, like all judges, human beings and the court operates on the human condition. Right? It doesn't operate exclusively on words on a page, but how they affect the human condition. And so to say to the Court, "You will affect the human condition well by upholding patents on technologies that bring new medicines to treat people who are desperately sick," is a useful thing to do as an advocate. And how could the [justices] have done other than recognize the whole point of the patent system is to create things that are good for people or to incent the creation of those things?

Now, it's also true that in the seventies, as I may have mentioned earlier, America was feeling a little sorry for itself because we suffered what President Carter called "economic malaise." We were recovering from the dire effects of the Arab oil embargo. We certainly were not being swamped with initial public offerings of high-technology-based companies. American industry was being hollowed out by the rise of manufacturing capability in other countries with cheaper labor, and so on. And so it was a sensible thing to say to the Court, this is a time to encourage innovation and a potentially vibrant new industry.

Hughes: The media, as you well know, was full of that kind of talk.

Kiley: Well, it was full of talk on both sides of the question. It was also full of expressions of concern over potential biohazard. Certainly, Mr. [Jeremy] Rifkin and his Peoples Business Commission, who opposed the grant of patents to new life forms, were making as much hay of that as they could.

Hughes: Yet Paul Berg and the group which had originally expressed concern about recombinant DNA research were by 1980 less concerned about the biohazard issue. It had simmered down.

Kiley: Well, certainly it had by that time, but it was still a prairie fire of concern amongst the lay public who fear what they don't understand. They don't generally understand science well, particularly fast-breaking new science, and so a right for exploitation by patenting would feed their fears.

U. S. Patent Office Handling of Biotechnology Patents

Hughes: Talk now about the [U.S.] Patent Office and its ability in terms of expertise and manpower to handle what was becoming a wave of patent applications in biotechnology.

Kiley: Well, the Patent Office attempts to staff with persons, called patent examiners, who are competent to review patent applications across the whole field of technology. So you have individual examiners with individual expertise in a particular technology. In the aggregate, you hope that you have examiners with expertise in all technologies. When a whole new science springs like Caliban from the cleft pine, the Patent Office can be caught unprepared. I believe it was in this case.

The moratorium to an extent gave it an opportunity to staff up, but the growth of patent applications in biotechnology has been exponential for the last several decades. I'm not confident the Patent Office has ever caught up. Today it's not uncommon to find patent

examiners with doctorates in molecular biology. I would venture to say there was not one such in the Patent Office when the biotechnology dam broke, and so they were obliged to scramble.

Now at the same time, there's something about the nature of biotechnology that asks challenging questions of the patent law, questions that are newer or richer or more bedeviling than other technologies. And I think that the patent law has been struggling to accommodate those questions and answer them ever since. They range from what is the appropriate breadth of protection that should be given for a particular piece of science that has been concretely demonstrated, to whether there should be--

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Kiley: --patents on what some call the universal commons of the gene pool. What constitutes reduction to practice? What to do about expressed sequence tags? What represents the complete conception of a gene isolated from nature--50 percent of it, 75 percent of it, all of it? Should the existing law on products of nature be changed in view of the emotion around patenting human genes? So on and so forth. All these issues in turn have been raised and hotly debated. Some are still being debated.

Hughes: Is the debate an attractant or a deterrent to attorneys?

Kiley: Aside from the fact that money is an attractant, certainly [those are] interesting questions. Consider all the interesting questions being raised in the wake of Decision 2000, the presidential election, and the attorneys being attracted like flies to honey. Well, so attorneys have been attracted to biotech in part because the questions are interesting but also because the stakes are high.

Genentech: Growing the Business

Intellectual Property and Contract Partnering

Hughes: Let's turn to Genentech. You presumably were mainly focused on intellectual property issues. Was that not the primary reason you were at Genentech?

Kiley: I think Genentech conceived intellectual property issues would be a very substantial part of its legal environment. That was an area in which I was somewhat competent. The company could treat with issues of general corporate law through outside counsel for some years to come. But I think it's fair to say corporate partnering and contract negotiation and so on were also clearly going to be an important part of Genentech's business. I had been active [in contract negotiation] on the company's behalf before I joined, and it continued to be a very big part of my activities afterwards.

Hughes: I've read about Swanson's goal to make Genentech a FIPCO.

Kiley: Fully integrated pharmaceutical company.

Hughes: Yes. How was intellectual property law and the contracts and the agreements that you were formulating tied to this drive?

Kiley: A FIPCO [is] a company that discovers, obtains approval for, manufactures, and sells ethical drugs for its own account. When I say ethical drugs, I mean proprietary drugs, and that implies patents. It turns out it's very hard to start a company and to succeed at doing that, because it takes an awful lot of money and an awful lot of time. At the end of the day, it's not worth doing unless you can have patents to justify the research. But in order to pull it off, you need to start with what nowadays is called platform technology--a technology that can lead to many products--and then you begin to sell off those products. We used to call it selling our children--to gain enough substance to promote the other children through the approval process. So patents are a necessary but not sufficient condition. You need also a lot of money.

One of my activities, and of other members of the legal group working with the marketing group, was to help raise that money, not from the sale of stock--that was left to the vice president for finance--but rather, if you will, through the sale of technology. It was clear that for a long time to come we wouldn't have the capability of marketing products in Europe, so sell the European rights. It was very difficult for any American company, certainly in the seventies, to think about marketing pharmaceutical products in Japan. So sell the Japanese rights and use, as we did in the case of the growth hormone, revenues from the sale of those rights to add to the substance required to get growth hormone approved in the United States for [Genentech's] own account. And so in effect, we were bootstrapping the company.

The other thing one does is sell things that just don't make sense for your company to hold onto in its then state, or the state that you can anticipate within your planning horizon--like insulin, like interferons, like ultimately the various agricultural and industrial applications that were bartered away to gain means to follow the main line toward the creation of a FIPCO.

Hughes: Did Genentech innovate this form of bootstrapping, or was it an approach that any young company, particularly with new technology, would use?

Kiley: Well, that it was certainly new in the extent to which it was practiced by Genentech and was permitted only because suddenly we had a very powerful toolkit that could do many things. I think those opportunities come largely only when one or a few parties suddenly find themselves in possession of something that's useful to many companies, indeed something that represents more than they can swallow themselves. And so you've got ample opportunity to share with others and in turn to gather the means to take what you keep all the way to the marketplace in the pharmaceutical industry.

Syntex and Alza: Positive and Negative Business Models

Kiley: Having said that, I remember Bob Swanson saying often that his positive role model was Syntex, because Syntex, the last company to pull itself into existence in the pharmaceutical industry prior to Genentech, had managed to hip off some of its technology to others, while keeping enough to grow on and to become a real company. For that reason, he wished to style Genentech after Syntex. On the other hand, he used to say Alza was his negative role model

because Alza, he thought, had given away too much to have sufficient left to grow a company. Now it's ironic, in the event, that Syntex stumbled when its patents on the products it had kept ran out and weren't replaced with new products, whereas Alza, in part because they got back much of the technology they had out-licensed in the first instance, has developed itself into a wonderful and very profitable company. So while Bob was prescient, he wasn't perfect.

Swanson: Organizational Development and Contract Negotiation

Hughes: [laughs] Was Swanson pulling on his business schooling background and his experience with Kleiner Perkins? Or on his native ingenuity?

Kiley: It's perhaps too cute to say that it came in equal measure from his genius and his ignorance. It's fair to say Bob was ignorant of how very difficult it is to make a drug company. He knew enough to think it would be hard, as it proved to be. But Bob had a lot of common sense, and I think his business training was the big contributor. His master's degree from the Sloan School was in, of all things, organizational development--not finance, not accounting, but organizational development. He had a genius for building an organization and at the same time keeping it focused.

Hughes: How tight a rein did he have over people like you?

Kiley: Not as tight as he thought. Indeed, there grew up a practice amongst some of us to keep Bob as far away from negotiations as we could because we thought the right things could be done more expeditiously if we kept Bob at bay. I think that was because Bob was somewhat of an uncompromising man, and compromise is essential in negotiation. I remember telling him once in reference to another employee that it is as important to manage up as it is to manage down. That is, you have to be able to manage your boss as well as your subordinates. He found that a very irritating proposition, but it's nevertheless, I think, right. The other feature of that is if you can keep your ace in the hole, you can maintain negotiating flexibility. If your chief executive officer is not present at the negotiation, it's a little easier to backwater if you find that you have agreed tentatively to something that you ought not to have.

Hughes: So you usually went into these negotiations without Bob?

Kiley: It was often the case that Bob would be employed in commencing discussions with another company, getting the attention of persons highly placed in it. Then we would do our best to retire him to the sidelines while the deal got largely done, and then return Bob to the scene to celebrate.

Hughes: He was compliant in this process?

Kiley: Well, he was. I don't mean to suggest that between times we weren't back at Genentech working very hard to keep Bob abreast of where things stood and trying to understand what his must-haves were so we could go achieve them.

Genentech: Patent Prosecution and Litigation

Hughes: Talk, please, about what it was like in those early days to work with scientists on a patent application.

Kiley: Well, it falls into two phases--one before and one after I joined Genentech. Before I joined Genentech, I was called on episodically, when a piece of science got done, to see what should be done about it in a patent context. That was true for somatostatin; it was true in the insulin case; it was true for growth hormone. I would come in when something had been cloned and ask the questions, How was it cloned? What was cloned? What other things could be expressed in a like manner? How broad should the patent application be? What truly has been the invention, as against the concrete embodiment that first illustrates the invention? And so that involves going into a dialogue with the scientists that deals only in part with what has been done, but also in substantial part with what could be done, given your possession of these techniques and that they are a product of your mind. Well, once you have an in-house patent staff, you have people who understand not only what has happened, but what is underway, and so they can be thinking in advance what science should be done in particular cases to best protect the commercial objective.

In both cases, I think what's really important is the ability to capture from scientists what they have to contribute without impeding the work of science, and so you need to be a quick study. You need to take them away from the bench long enough to get high enough up on the learning curve to do your job and before you reach their threshold of irritation. Patent attorneys generally try to develop those skills.

The most important thing to know is what you don't know that you need to know, so that you can ask the question and get the information and get out of the scientist's face and let him or her get back to the bench. I must say that before long I became so enmeshed in the corporate partnering side of things and ultimately in the litigation side of things that I had to give over preparing and prosecuting patent applications to other hires. Indeed, the last patent application I ever prepared in my life was the application for Genentech's alpha interferons done in July of 1980.

Hughes: Oh, really?

Kiley: Now, for twenty years I've been involved in biotechnology patent law and practice, and I haven't prepared a patent application in all that time. But I did weigh in from time to time when applications prepared by others needed to be pushed over the goal line, most notably in the tPA [tissue plasminogen activator] case and the interferon gamma case.

Gamma Interferon

Hughes: What do you mean by "pushed over the goal line?"

Kiley: Well, I'll illustrate with reference to interferon gamma. Genentech announced the cloning of interferon gamma, and just before it did, Genentech filed a patent application for what it believed to be the sequence of DNA that encodes interferon gamma. It turned out the inventors had guessed wrong as to the start point for the DNA and the corresponding amino acid sequence, with the result that what was first described, both in the publication and in the patent application in so many terms, was not interferon gamma, but interferon gamma with extra amino acids at its N-terminus--cystine, tyrosine, cystine. Not only had we claimed too much of the molecule, but the pieces that were added turned out to be real headaches because they formed cross links to other molecules. And while I didn't prepare that patent application, once we realized what had been done, I took charge of prosecuting it.

It turns out the scientists had illustrated the expression of gamma interferon not only in *E. coli* bacteria--which did what they were told and made the wrong thing--but also in a transient expression system, called a COS cell. And while the scientists had been fooled, the COS cell was not, and it knew how to process the DNA so as to do away with the extra bit.

Now in patent law, there is something called the doctrine of inherency which says you can add to an already filed patent application new words not earlier present to describe something that would have inherently arisen through the practice of what is described. And what inherently arose by virtue of the genius of the COS cell was the right stuff, and so now we could add to the patent in so many terms what had already been implicit in it, albeit unknown to us. So that was a question of snatching victory from the jaws of defeat, if you will.

Tissue Plasminogen Activator

Kiley: Another instance of my involvement in the patent prosecution process arose in the case of tPA, where we had pending in the United States an application for, amongst other things, systems capable of expressing tPA, Genentech's then flagship product. In a litigation in the United Kingdom the Wellcome Trust challenged the corresponding British patent. Well, we lost in Britain. Both the trial court and later the appellate court heaped obloquy on our entitlement to a patent of appropriate breadth. The patent application was still pending in the United States.

Patent applicants have a duty of candor to the United States Patent Office to tell the Office everything known to them, or which should be known to them, which the examiner might consider important for him or her to know before granting a patent. So it fell to me to come back from Great Britain with all of these decisions against us by the several courts and all the testimony against the patent from witnesses from the Genetics Institute and Wellcome Trust and their respective expert witnesses, and put it in front of the Patent Office and say, "Here it is, and it doesn't matter. We're entitled to a patent--not a narrow patent, but a broad one." And so that became one of the last tasks I performed as a full-time employee of Genentech. The patent was granted, and on the day it was granted, we sued the Wellcome interests in Delaware and ultimately prevailed, and they left the tPA business worldwide.

Hughes: Was it a given that you would sue as soon as the patent issued?

Kiley: I think it was necessary we do so, in part because it gave us the opportunity to choose the forum. It was clear there was a controversy between the companies, and it might have been open to Wellcome, had the patent issued and we not sued it in Delaware, for Wellcome to sue us elsewhere in the United States, perhaps in a forum less neutral toward Genentech than Delaware could have been expected to be. For example, in the Carolinas where Burroughs-Wellcome, a subsidiary, did a lot of business.

I may say, despite all of the efforts we at Genentech made to put in front of the United States Patent Office every bad thing that was said about our entitlement to a patent, in the Delaware trial, I was the victim of the usual knee-jerk accusation of misconduct before the Patent Office--

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Kiley: --and that the patent should be held invalid because of that misconduct. Indeed, the attorney who represented Wellcome in that matter has been quoted as having said the tPA case represented the clearest case of patent fraud he'd ever seen in his career, and if he couldn't persuade the court to that effect, he would resign from the practice. [It was] somewhat reminiscent of Bobby Kennedy having said, while serving in the Justice Department, he would jump from the Capitol dome if he couldn't convict Jimmy Hoffa of a crime. After Ed Bennett Williams got Hoffa off, Mr. Kennedy failed to follow through, and I think Wellcome's lawyer did as well. In the event, the jury found, and found very quickly, no misconduct on Genentech's part and upheld our patent as both valid and infringed by Wellcome.

Hughes: Was that Genentech's first big case?

Kiley: I'm inclined to believe it was the first time Genentech initiated litigation against a competitor on one of its patents. It was certainly not the first time Genentech was involved in litigation. Indeed, in Genentech's early days, it was made to run a gantlet of patent litigation brought against it by larger companies on what I regarded as improvidently granted patents, oftentimes I think with a view toward imposing leverage on Genentech in the hopes that Genentech would cough up valuable rights in return for peace--such as, for example, rights to tissue plasminogen activator.

Hughes: Were your opponents usually other biotech companies?

Kiley: No, almost invariably I would say they were big pharma companies--Eli Lilly; Abbott Laboratories; Rhone-Poulenc Rorer, although that [last] litigation may have been styled Scripps [Research Institute] versus Genentech, as Rorer's rights came from Scripps. And of course the first Wellcome case itself, because the litigation was instituted by Wellcome against Genentech in opposition to the grant of Genentech's British patent, rather than Genentech's having initiated it against Wellcome. Of course, we answered in kind when we did go after them in Delaware once our U.S. patent was issued.

Human Growth Hormone: The Hoffmann-La Roche Suit

Hughes: Let's talk about the other important litigations that you mentioned off-tape.

Kiley: Well, let me just briefly characterize a few of these before getting into the more interesting subject of the Lilly litigation. Both Abbott and Roche expressed to us an interest in gaining rights under our tissue plasminogen activator properties. This was the clot-dissolving heart drug.

Hughes: They came to Genentech?

Kiley: Yes, and ultimately we decided rather than grant rights to those parties, to divide them up amongst Japanese and European companies and keep the North American rights for ourselves. I think it's fair to say that both Roche and Abbott were unhappy at that.

Well the first thing that happened, out of the blue Genentech was sued by Hoffmann- La Roche on a patent issued to a professor C. H. Li of the Hormone Research Institute affiliated with the University of California [San Francisco]. That was a patent that purported to claim "synthetic human growth hormone"--period, full stop. It resulted from work that Dr. Li had done in an attempt at synthesis of human growth hormone, amino acid by amino acid, using peptide chemistry. And having got what he thought was growth hormone by that route, he then got a patent claim to synthetic growth hormone. And of course the assertion was now made that synthetic growth hormone encompassed recombinant growth hormone and Genentech was infringing that.

We found a chapter in a book Dr. Li had edited which was about all the problems that arise when you try to make a complex molecule by amino acid serial synthesis. The author calculated if you tried to make something as large as human growth hormone, you would wind up with an untractable mixture of nearly a billion different molecules. So in our view, it would be proper to construe synthetic growth hormone as meaning what it meant to Dr. Li at the time he filed his patent application and long before recombinant DNA was envisioned by anyone. Moreover, his patent itself was not enabling; it couldn't teach anyone how to make growth hormone. So that case ultimately went away.

Hughes: You mean it wasn't litigated?

Kiley: It was litigated until Hoffmann-La Roche quit litigating.

Hughes: Was that your case?

Kiley: I was involved as inside counsel. We were represented outside by others.

Urokinase: The Abbott Laboratories Suit

Kiley: The Abbott case was very much of a kind to that. We had a project at one time with Chemie Grunenthal to make a plasminogen activator other than tissue plasminogen activator. It was a product called urokinase. Well, it turned out someone had purported to have cloned urokinase, but the technique was so bad the applicant asserted in his application for patent that he had managed to make a cDNA [complementary DNA] library having not more than eight members, from which, *mirabile dictu*, he had managed to pluck more than one cDNA purporting, according to him, to express urokinase. And on the basis of that work, which I thought shoddy, the Patent Office had given him a patent claim that in effect read a recombinant plasminogen activator, which covered not only urokinase but tPA.

Abbott sued us for infringement of that patent, asserting that our tPA practice infringed their patent claim, and at the same time made it very clear all of this could be settled were we to yield up tPA rights to them. And that case went away well before trial with no payment by Genentech.

Factor VIII: Scripps Research Institute

Kiley: The factor VIII litigation was somewhat different, but was illustrative of what happens in patents when you find not a new drug, but a new way of making an "old" drug. Like insulin, or more appropriately, like human growth hormone, so factor VIII was not necessarily a new drug in Genentech's hands; rather we made a new system for making larger quantities of putatively more pure factor VIII than had hitherto been available.

Hughes: So you were trying to patent the process?

Kiley: Well, the issue was not so much what we were trying to patent, although we did file applications on the recombinant system. The issue was what others had patented that might dominate us. Factor VIII is also called anti-hemophiliac factor. It's used to help hemophiliacs clot. Rhone-Poulenc Rorer sold factor VIII purified from donor blood under the rubric "Monoclate" and had managed to get a patent on a composition of matter described as factor VIII of a purity greater than X percent. Their contribution lay, according to their patent, in having devised a better method for purifying donor factor VIII, which yielded a patent claim purporting to cover any factor VIII from purity X percent up to completely pure factor VIII. And that patent, it was alleged, would be infringed by recombinant factor VIII. Ultimately that case was settled as well.

Human Growth Hormone: The Eli Lilly Suit

Kiley: Probably the most bitterly fought litigation during my days at Genentech was the litigation commenced in the mid-80s between the company and its erstwhile partner, Eli Lilly, over

growth hormone and related subjects outside the scope of the contract between Genentech and Lilly relating to human insulin.

Hughes: Why so bitter?

Kiley: Well, bitter I think because it was a falling out amongst partners and so had elements of divorce in it, although Lilly continued to pay royalty on its insulin sales through the full term of its agreement with the company. Partly bitter because I believe Lilly from early days regarded with some disdain what it took to be hubris on Genentech's part around Genentech's contribution to human insulin (which was so much a part of the history and lore of Eli Lilly as a company). Also because Lilly had sponsored the human growth hormone research at UC San Francisco, a race Genentech clearly won in competition with Lilly; in part because broad patents had been granted to Genentech that interdicted in terms broad areas of interest to Lilly but not available to it under its arrangement with Genentech, at a time when Lilly was clearly restyling itself as a biotechnology-based company.

Hughes: And doing gene-splicing in house?

Kiley: Certainly building great capability in that area, and yes, ultimately doing so. Lilly, for example, had the frank ambition to be in the growth hormone business. Ultimately it was.

Well, the litigation commenced with a suit by Lilly seeking the invalidation of some of the Riggs-Itakura patents. A time came when Genentech responded by counterclaiming for Lilly misappropriation of Genentech property. That arose in this way: Genentech's contract with Lilly required that we develop and provide to Lilly microbial systems for the production of human insulin. We recognized we would be putting into Lilly's hands microbial machinery that could be converted to other uses. We wished to protect ourselves against Lilly's doing that. So we said in the agreement with Lilly we would deliver that material for use "only," quote unquote, in connection with their production of human insulin. In the event, we learned that Lilly had used the microbial machinery to produce a form of human growth hormone.

They used it to produce a form of human growth hormone that lacked N-terminal methionine, which at that time was present on the only growth hormone Genentech was selling. Having used the microbial machinery to produce this product different in that respect from Genentech's, Lilly was able to obtain orphan drug protection from the FDA and prevent Genentech for a period of years from putting onto the market its own version of methionine-free human growth hormone. That gave Lilly a considerable leg up in the human growth hormone market. Genentech thought it had been grievously injured by a clear arrogation by Lilly of property that didn't belong to it.

Lilly's defense was amongst other things that the nature of the various contractual constraints imposed on it by the Humulin [human growth hormone] agreement were anti-competitive to the point of amounting to patent misuse, rendering our patents unenforceable. In any event, they claimed the word "only" in the agreement could not possibly mean "only," and so that litigation went ahead in various venues. There were cases in San Francisco; there were cases in Indiana; there was parallel litigation attacking the patents in Great Britain. The several University of California lawsuits got enmeshed in all of that. UC was suing Genentech in respect of growth hormone and Lilly in respect of human insulin. And all of this under the rules of multi-district litigation got added into one great big puddle of complexity.

Hughes: What was your involvement?

Kiley: While I was deposed at great length over various issues arising from our prosecution of the Riggs-Itakura patents, and so on, and the Humulin agreement that Bob Swanson and I negotiated, I left management of the litigation to Brian Cunningham, then general counsel of the company, because of my almost all-absorbing involvement in the tPA litigation and related subjects.

Hughes: Was that fortuitous in a way?

Kiley: No, I think it was sensible. It was simply a division of labor at a time when Genentech had a little more litigation going than could be managed by one person. I'm happy to report that the Genentech-Lilly litigation was ultimately settled with, I am told, the payment of a very large sum of money by Lilly to Genentech.

Hughes: You don't know the amount?

Kiley: I'm not sure that the full amount has ever been announced.

Hughes: It was sizeable enough--

Kiley: More money than I will ever see in my lifetime.

tPA: The Wellcome Trust Litigations

tPA as a Possible Product

Hughes: [tape interruption] Would you like to say more about tPA, which you mentioned as Genentech's flagship product?

Kiley: I referred earlier to the litigation in Delaware and in the United Kingdom in the context of its impact on patent prosecution. Certainly, in view of the centrality of tPA to Genentech as it stood at the time I left its employ, it's worth looking more closely into that litigation. tPA was identified as an opportunity for Genentech by a young woman, a molecular biologist and an employee of Genentech, whose name is Diane Pennica. Diane was attending a conference in Lausanne, Switzerland when she met a fellow by the name of Desiré Collen.

Desiré had been isolating minute quantities of a product he dubbed tissue plasminogen activator from cells obtained from one of his patients at the University of Leuven in Belgium. Through laborious culture of these cells, which were not recombinant cells in any sense of the word, he had managed to get together enough of this protein to show in a single patient it would dissolve peripheral arterial clots. It did so by activating a substance called plasminogen, which in turn through a cascade of events could break apart the scaffolding that holds a clot together.

Diane came back to Genentech and suggested this agent, called for short tPA, might be an interesting candidate for production through recombinant means because it was not available in practicable quantities, certainly not practicable for more than a handful of patients, from Dr. Collen's technology. Well, Bob Byrnes and I stopped in to see Desiré in Belgium on our way home from other adventures in Europe and very quickly negotiated with Dr. Collen and with his institution an agreement under which Genentech would have exclusive rights to patent applications he had filed on tissue plasminogen activator as a purified substance or composition of matter. At the same time we entered into a collaboration with him under which he would supply Genentech with messenger RNA or cells that could be the raw material for an attempt to clone the gene that underlay his protein and express it in the form of tissue plasminogen activator.

That proved to be a very difficult problem. Indeed, after we carried it off, I made an effort to determine just how hard it had been to do so. To that end, I took a half dozen of the leading molecular biologists at Genentech offsite at Lake Tahoe for a very long weekend. We aimed to read every cDNA cloning paper ever published in the English language and to rank order the tPA project in terms of difficulty against all prior cloning efforts. We were able to satisfy ourselves, and indeed the Patent Office of the United States, that the tPA cloning effort represented the highest level of achievement to that time in any cDNA cloning, whether measured from the standpoint of what was known about the amino acid sequence in advance, or the size of the protein, or the rarity of the messenger RNA in the biological sample.

The Wellcome Suit in the United Kingdom

Kiley: Ultimately we obtained a patent in the United Kingdom, and that quickly became the subject of litigation with the Wellcome Trust, which had fallen heir to rights held earlier on by Baxter Health Care, who in turn had obtained them from Genetics Institute in Boston. And we charged Wellcome with patent infringement. The patent infringement issue first came up in the United Kingdom. So issue was joined in the Royal Halls of Justice, or as I later came to call them, the Royal Halls of Injustice, and we set about preparing for a patent contest on Wellcome's home ground.

Hughes: Were you directly involved in this case?

Kiley: I was. Indeed, I learned, I can't recall how--there was a patent barrister who was regarded as preeminent amongst his peers in the United Kingdom--and I went to Gray's Inn, one of the four Inns of Court in London, and basically knocked on his door and got his clerk to give me an appointment with him. His name was Stephen Gratwick, and he could get three syllables out of a letter "P." Well, this was highly unusual because ordinarily you've got to approach a solicitor. The solicitor in turn will brief a barrister, or rather the barrister's clerk, who will decide whether the barrister's time will be permitted to be taken up by the solicitor, importuning him to represent a client.

Hughes: Did you know that procedure at the time?

Kiley: I don't know if I knew it or not, but I wasn't deterred by it [laughter], because I thought I could capture Mr. Gratwick's attention through the very novelty and excitement of the technology, and that proved to be a good strategy.

Mr. Gratwick agreed to represent us, described to me the convenience of having a solicitor involved under the British practice [laughs] and recommended that I engage one. He recommended Simon Cooke of a firm then known as Bristows, Cooke, and Carpmael which a few years ago celebrated its one hundred fiftieth anniversary, an occasion that the Queen herself attended. And so I hired Simon, and we got to work getting ready for that trial. Likewise, Wellcome got to work, and Genetics Institute, [which] had a stake in the matter, turned its attention toward it.

Well, it turned out the Brits had just rewritten their Patents Act from stem to stern. This would be the first patent trial involving biotechnology; it would be the last patent trial held before the chief patents judge in the United Kingdom, who was about to retire; and ultimately it would be the first patent case of any kind to be reviewed by the British court of appeals under the new Patents Act. So in many respects we were (a), in the spotlight and (b), traveling uncharted waters, and (c), optimistic if we thought we were going to win against a revered philanthropic British institution, as the Wellcome Trust then was, in the last and crowning achievement in a British patent judge's career, our being mere upstart colonials.

I thought I should hire an expert witness, and I approached Sydney Brenner of Britain's Medical Research Council who was known to me from 1980 when I gave a talk at Cold Spring Harbor [Laboratories]. Over a long dinner at Claridge's in which various bottles of wine were emptied, I persuaded Sydney to appear as an expert if his boss, Sir something would permit. Some time passed, and Sydney called me with the bad news. He had taken it up before his boss and, according to Sydney, his boss had said if Genentech won against Wellcome there would be dreadful political ramifications, "So Sydney, I am adamant. You shall--

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Kiley: --not do it." "Sydney," I said, "You have left me in the lurch. You're going to have to help me obtain some other expert." "How about Paul Berg," he said. "Well," I said, "I suppose Paul has some expertise in molecular biology. [laughter] I wonder if you would have a conversation with him."

Sydney did so, at least to the point of getting me an audience with Paul. And I did succeed in getting Paul to go along. Indeed, I will never forget on the day trial was to open, I overheard Mr. Gratwick, my barrister, in conversation with Robin James, Wellcome's barrister. James asked, "I've heard a rumor. Will you use Berg?" And Gratwick replied, the Falklands war having just concluded, "Oh, yes, if one has an Exocet [missile], one should deploy it." [laughter]

Paul, I think, accepted the task first because he'd never been an expert witness in a patent matter, and so I succeeded in appealing to him with the novelty of it; secondly, because Paul had had an interest in the patent implications of biotechnology from the Asilomar conference days; thirdly, because by that time Paul was involved in DNAX, a private company, and thought it important in appropriate circumstances patents be upheld against attack if they were to prop up biotechnology's development.

Now, I don't think Paul fully knew what he was getting into, and perhaps I could have been more explicit in describing that, but in the event I did not. I didn't think I could get Paul to sit down and read all the cDNA cloning papers that had ever been written, by way of getting ready for the trial. I decided I would have to get someone else to do that, and I hired George Stark.

George was then with the Imperial Cancer Research Fund, conveniently just across Lincoln's Inn Field from the offices of my solicitor in London. I sidled up to George with some help from Paul Berg and said I would like some help from George in understanding what things were easy and what things were hard and why at the time tPA was cloned. This was all in aid of proving what we had done was deserving of a patent. And George, again for the novelty of it, was happy to help out, particularly as I told him he'd be working with his pal, Paul Berg. And it wasn't until much later in the process that I was obliged to tell George now he would have to read 250 cDNA cloning papers, which he was kind enough to do. By that time of course he was fully hooked and wound in.

So the notion became, George will get on the stand and describe, having gone through this exercise at our behest, just how hard it was to clone tPA. Paul would come in and, speaking from his great height, pour holy water on our patent in various ways, and we would win. And indeed, at the trial Stark and Berg were immensely persuasive of the validity of our patent; to the point where the trial judge, in his nearly incomprehensible opinion after the conclusion of the trial, was obliged to admit what had been done seemed well beyond the skill of the ordinary worker. Ultimately, there was an appeal because Genentech lost, not because what we had done was regarded as easy, but rather [according] to the trial judge, we had claimed too broadly given what had been done. We had patent claims that were "greedy and overreaching"--his terms. And so for that reason, the patent was held not valid. And we appealed.

The appeal was to go to a three-judge court, and did. And that court decided in view of the general novelty of the technology area it would like to have a court expert to help it answer science questions and asked the parties to generate a list of experts acceptable to them. Wellcome did so, and of all things Sydney Brenner's name was on the Wellcome list. Well, I confessed my satisfaction with having Sydney serve in that capacity, and he ultimately did. And I guess I forgot to mention [at the time] the conversations I'd had earlier with Sydney. But it didn't matter because the court of appeal was scrupulous in using Sydney only to understand science and wasn't willing to hear him opine on questions of patent law, even had he wished to do so. I doubt very much if he would have so wished. That was an interesting sidelight of that whole matter.

I believe, and I think the trial transcript would illustrate, Genentech scored knockout victories over every Genetics Institute and Wellcome Trust witness that came under cross examination in trial. Our witnesses excelled. I think by and large, their witnesses were confounded. And I predicted, rashly in the event, a Genentech victory.

I was awakened in the middle of the night, a week or so after returning from London, with the news that Genentech had gone down. The judge issued a nearly unintelligible opinion. Ultimately, no judge of the appellate court agreed with anything the trial judge said. Ultimately, no judge of the appellate court agreed with anything any other judge of the appellate court had to say, while construing the first case to come before them under the new Patents Act, the first biotech case they'd ever seen, and the trial judge's last case. But when you

added up all the votes at the end of the day, a way had been found for Genentech to lose on this ground or that ground.

That was very bad news, as it came at a time when it was clear that tPA would be the product that would make Genentech a large company. Here a patent had been held invalid overseas, with at least the suggestion the same result would follow in the United States, if we ever succeeded in getting a patent, which to that time we had not. So that was grim news.

In Great Britain, when you go to an appellate court, there is no transcript or written record to lay before the court for its reading. Instead, counsel has to stand before the court and read to them all of the evidence, and from so much of the transcript as they wish. And so a trial that took seven or eight days took three weeks on appeal, while all of this was read to the court. And I must say it was all rather mind numbing and unsettling to see these judges sitting there and exercising their minds and their curiosity over what to make of the new Patent Act in this new context and so on.

So ultimately we found one judge saying such things as, "People in molecular biology ordinarily have doctorates. In order to get a doctorate, you must demonstrate your capacity for innovation for original research. Therefore the ordinarily skilled person in molecular biology already has inventive capacity. So it is for us to measure how much more invention than inventiveness is required to justify a patent. Where is the genius?" And of course our courts have for decades understood that the "spark of genius" is not the proper test.

The court, in the view of one of the judges, should find that Genentech had claimed too broadly because it claimed not only tPA made from a particular gene, but also tPA made from other genes with a different amino acid. It developed the accused gene differed from ours in respect of a single nucleotide, which led to the accused product having a single amino acid difference from ours, out of some 576. And because in patenting we had sought to encompass such possibilities, the patent claim had been written too broad[ly] and that was called "greedy and overreaching."

What the court didn't know, because Wellcome purported to admit infringement, was their accused product was one nucleotide different than ours, and that difference sprang from a reading error when the reverse transcription enzyme hiccuped as it was making their cDNA. So here we are having to deal with a situation of that kind. There is Wellcome having concealed [by admitting infringement and mooting the issue] how close their product was, very tactically. And the court giving them a pass because we had overreached to the point of having written a claim that would not be avoided by a single nucleotide difference. All very unsettling.

Defenses that were accepted by the court had never been presaged in the filings Wellcome had lodged with the court, as British rules require. We claimed unfair. The court said, "Certainly with counsel as sophisticated as those present and in a matter of such import, it would be inappropriate to place undue emphasis on mere formalities." Or as I later said, "This is a very important matter; therefore Britannia waives the rules." [laughter] That was a line in a paper I later wrote called a "Tale of Two Trials," in which I compared the British trial and the later American trial. It's somewhat tongue-in-cheek and was done for a presentation to a society of expatriate British barristers here in San Francisco. I had a lot of fun doing it.

Hughes: They had a lot of fun hearing it, I imagine.

Kiley: Well, it's always more fun to talk about it after all the battles are over and the war has been won.

Hughes: What circumstances explain the court's irregular approach?

Kiley: I harbor a suspicion that amongst some quarters of British society and within British institutions there is a residuum of disdain for jumped-up people and jumped-up companies which are seen as more full of themselves than any newly made person or company or republic ought to be. Sometimes one runs into that in Great Britain. At the same time, I said earlier there is something about biotechnology that challenges patent law, either by confounding established principles or demanding evolution of new principles. It is a lot to ask of a court, particularly a court of appeals with a record in place, to get everything right when the rules are new and haven't been interpreted by past cases, when the technology is remarkably new, and the more so when the court is composed of people with no special technological expertise. But that's a problem one has in all patent situations.

Failing to Patent Monoclonal Antibody Technology

Hughes: Do you suspect that there could have been some bias in Britain against patenting in this field? I'm thinking of the [Cesar] Milstein monoclonal antibody episode in which he inquired about patenting the procedure and was turned down.

Kiley: That was [Georges] Kohler and Milstein's work that led to a Nobel Prize for their development of hybridoma technology. The work was done for the Medical Research Council in Great Britain.

Hughes: It may have been the Medical Research Council that turned down the patenting proposal.

Kiley: It was. I met the man who said no to it, much vilified in the wake. Indeed, Maggie Thatcher is quoted as having said, "I will never forgive you for the hybridomas," she being a biologist or biochemist herself and a person interested in patents. Well, so here we have Britain perhaps rankled at the fact it missed getting patents on a major contribution of its scientific establishment. And now comes a pushy American company, seeking to impose its patents on a British institution at a time when biotech is getting very hot, and it looks as if Britain has missed the boat. Those things shouldn't influence jurists. I doubt if they consciously did. [But] we're all human beings and we all bring our philosophies to bear on problems we're obliged to solve.

Hughes: Did your acquaintance give an explanation for turning down the Kohler-Milstein patent possibility?

Kiley: I think he did, and I don't recall the justification. Nowadays, one says, "If there's doubt, file the patent application--on everything." And perhaps we weren't all as smart in the earliest days of biotechnology. There are also budgets to deal with.

Hughes: That discovery was made in 1975. There was no strong history of patenting in bioscience at that time.

Kiley: Well, consider how very nearly the Boyer-Cohen patent [application] escaped the statutory deadline in the United States.

Hughes: Yes, one week, it was.

Kiley: And no foreign patents have been filed at all.

Hughes: Right.

A Surfeit of Patents in Biotechnology

Kiley: On the other hand, I think things have gone too far in the other direction now. We're cluttering up the landscape with such a dense thicket of patents that before long I fear companies will be caught like flies in amber and unable to move in any direction. When opposing the National Institutes of Health patent filing on thousands of expressed sequence tags, I questioned their utility.

There is a dark side to the patent system. The point of patents is to encourage innovation. To the extent we insist on patenting the very tools of science, the very raw materials on which scientists operate, we run the risk of standing the patent system on its head and discouraging rather than promoting the creation of new things.

Hughes: Your warning seems to have fallen on deaf ears.

Kiley: Well, I have speculated there is a reason for that. The patent bar is unlike the personal injury bar. The personal injury bar is controlled by two distinct communities, plaintiff's trial lawyers and insurance defense lawyers. And whenever one of those communities goes too far, the countervailing community is there to pull it back, and so some rough equipoise is achieved, or at least one hopes for that.

In the patent case, first I would say on the order of 90 percent of patent attorneys never see the inside of a courtroom. They make their living by writing and prosecuting patent applications and obtaining patents. And to that great majority of the patent bar, the patent is regarded as the end product rather than, as I now see it, something that helps medicine become an end product so someone can get well. And so the more patents the better, for that part of the patent bar. Patents are the goal. And the more patent applications one files the more money one makes because one is charging for his time.

The rest of the patent bar are the patent trial lawyers. And unlike the personal injury bar, the patent trial lawyers work both sides of the street. Who is suing on a patent one day may in another case, the next day, be opposing a suit on a patent. Who is claiming a patent to be valid and infringed one day may be claiming a different patent to be invalid and not infringed on the next. And so there is no cohesive group within the patent trial bar that is likely to stand up and

say the pendulum has swung too far toward broad patents or patents of suspect utility and their enforcement. Consequently, what happens is we're choking on patents.

Hughes: But surely the legal system has some form of checks and balances other than this internal one.

Kiley: Well, in terms, an adversarial system has checks and balances. But I don't think the checks have been as effective as they once were in view of the pendulum having swung very far toward the unquestioning acceptance of patents and undue deference to an overloaded Patent Office. The standard for invalidating a patent nowadays is clear and convincing evidence. That's a very high standard. It nearly attains proof beyond a reasonable doubt.

Since the various circuit courts lost their appellate jurisdiction (which has been collected into the Court of Appeals for the Federal Circuit), there are not now dissenting circuit courts around the country taking decisions in conflict to the Supreme Court for resolution. There is one patent appellate court, in effect. And I think statistics will show that court itself has come to regard patents as a good in themselves, and it's been decidedly pro-patent.

Hughes: Do you know what the context for that might be?

Kiley: In part it's a reaction to a time when courts were populated by trustbusters from the Roosevelt administration who were very suspicious of patents. They went too far against patents. Now the pendulum has swung back. One must admit at a time when technology is flourishing in the United States and is increasingly the reason for our economic well-being, it might be right that aggressive grant and enforcement of patents has something to do with that.

Having said that, I still think in the biotechnology case, patents can be very problematic, however necessary they are to protect a particular drug and the investment required to get it approved. The science in biotechnology starts at the most fundamental levels and proceeds upward through a journey of a thousand miles to get to a medicine. Whether it's pathway definition or target isolation or target validation or DNA expression or the assignment of function or expression in scaleable quantities or the antibodies or other reagents that one passes through in this whole course of research, at every step along the way patents are being sought and issued.

As I pointed out in an article in *Science*,[1] the point is not to protect a particular step on the journey, but rather to control the economic outcome of the end of the journey. At least that is the point in many cases. And so people are getting all these traps for the unwary in which they patent the earliest stages of research and the raw materials of research and lie in wait until somebody makes the long journey toward the creation of something of tangible benefit in the marketplace and then they spring and say, "Gotcha. There's my patent."

The other thing is that patent litigation is very expensive because it's so fact centered, because so much time has to be devoted to establishing the milieu in which particular inventions occur and how they relate to the whole past history of the development of the branch of technology, and is filled with contentious experts on both sides of every issue. And so the

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[1]Thomas D. Kiley, "Patents on Random Complementary DNA Fragments?," *Science* 257 (1992): 915-18.

more patents there are, the more opportunity there is for mischief. There used to be trial lawyers; now they're called litigators. And in my mind the difference is a trial lawyer seeks an adjudication of what is right, whereas a litigator is less focused on the end game than on the process itself, which by its duration and complexity can become a club in the hands of powerful interests.

Hughes: How can this situation be turned around?

Kiley: [pause] One of the great evils of the patent system that is seldom commented on and which is deeply lodged in the law, perhaps to the point where it's unchangeable, is the notion if you have created a composition of matter, a substance, or a thing, you may control that for all purposes, even if at the time of its creation you know of only one purpose for which it can be used. So you isolate from nature a particular genetic sequence, and you say, "This came from a brain. I can use this sequence to distinguish brain tissue from other tissue forensically. Therefore, I claim this gene as a new composition of matter when present in pure form. And by the way, if it ever turns out to encode a protein useful in the treatment of Alzheimer's, I'll be able to control that, too."

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Kiley: You can't make that protein via recombinant technology, because to do so you have to infringe my patent on this gene.

Patents in Biotechnology: Issues Raised

Patenting Nature

Kiley: There's another aspect of this mentioned all the time, and that is patenting things that exist in nature. To the lay ear, that sounds inappropriate, but patent lawyers have been comfortable with that for the longest time. Because while something may exist in the *gemisch* of nature, it's no good to anyone until it's discovered, isolated in a form in which it never existed before, that is, in pure form. The courts have held something that exists in nature is nevertheless novel when it's produced in a different form, that is, pure form.

Well, perhaps, if all that was revisited, the burden of patents could be reduced. Having said that, reasonable people probably conclude that it goes too far. For example, tPA exists in nature, but not in pure form. If you couldn't patent a natural substance, Genentech couldn't have patented tPA. If Genentech couldn't patent tPA, it wouldn't have spent the millions of dollars required to get it approved as a product, and scores of thousands of people now alive would be dead. So that is another aspect of patents that is susceptible to abuse, but for which no ready solution presents itself.

Utility

Kiley: Here's another one. The patent law requires that to be patentable, a new thing must be useful. The Supreme Court held in [*Brenner v. Manson*] in 1960 the patent is the reward not for the hunt, but for its successful conclusion--that things useful or interesting only as scientific curiosities cannot themselves be patented, but rather what is required is tangible benefit in specifically available form. Now what does that mean? Well, no one seems to know. That case nowadays is largely disregarded as a case in which absolutely no utility was described for the chemical compounds sought to be patented, other than their use as an object of research. But if you can say so much as, "Use my brain sequence to distinguish tissues that are not from brain," that's a utility of some kind. It's a scintilla or an iota of utility, and that's all that's required.

Well, if that is the law, then the door is wide open for people to assign the most ephemeral utilities to each new DNA that comes out of the gene sequencing effort and to take patents on it, and then wait like a spider in its web for some hard-working fly to come along, who, for example, has learned principles of flight to carry this gene up into real utility as a medicine or a medicine-providing substance, and then devour it.

Hughes: That hasn't happened yet, has it, because we're not far enough along in the process?

Kiley: I would not agree with that; it has happened. In fact, it's happened, I would say, to me. But what to do about that problem? Well, you have to draw the line of utility. There should be a bright line between what's useful and what's not. Well, that's very hard for a legislature to do, viewing the subject at large. It's almost impossible for a court to do, taking cases one at a time. And so in my view, the courts have largely conceded their inability to answer the question and are willing to accept the most spare imaginable utility.

Deleterious Effects of Patent Barriers

Kiley: So what's gone out of the law? Well, things have to be new, but they're new even if they're present in nature. Things have to be useful, but a scintilla of utility is all that's required. Things have to be unobvious, but at least one British appellate court tells us they're not clear what that means other than more inventive than inventive. And so we're all left at sea. And meanwhile, patents arise around the landscape like locusts and might strip the storerooms of laboratories around the world clean of what they need to get things done.

Hughes: I would think that this situation would be a huge concern to young companies.

Kiley: I believe it is. And most particularly because the overhang of these patents, perhaps granted improvidently by an overworked Patent Office or undertrained patent examiners, may prevent those companies getting financed. Investors don't wait to see if you win or lose a patent lawsuit before they invest. They assume that you will lose if there is a patent that in terms and on passing inspection seems to interdict what you're doing, without regard to whether that patent is

valid or not. Young companies today confront such a cluttered patent landscape it's often very difficult for them to show an investor how they thread their way through to the light.

Hughes: Hasn't Genentech been accused of doing something similar? Didn't Genentech clutter up the landscape--using your phrase--for the young companies that were to follow? I'm trying to determine whether that was a matter of history or a deliberate tactic.

Kiley: I will say as to Genentech that it clearly was a pioneer, and on that basis clearly was entitled to claim broadly. Over time, Genentech used its broader patents in part to protect the particular subjects that it had chosen to take into the clinic and into the marketplace, and at the same time made available licenses under those patents for all other products at very modest royalties. So to the extent its product-development ox wasn't being gored, it acted like Stanford University did in respect to the Boyer-Cohen patents.

Now, without commenting in particular on Genentech's patent policies, I would say the one practice that I think has become widespread amongst companies that may share my views about the avalanche of patents in this area is that they don't know what to do about it either, other than to keep filing on everything conceivable, in part so that someone else won't before them, and in part so that they'll have as much throw weight as a future opponent in some patent version of mutually assured destruction.

Hughes: A vicious circle.

Kiley: So things can be handled on a negotiated basis. And I harbor the suspicion that a lot of the patenting that goes on nowadays is patenting for that purpose.

Hughes: That was not true when you were practicing?

Kiley: Oh, I think it's probably been true in some industries for quite a long time.

Hughes: Yes, early in this century, some of the big corporations were accused of blocking the field deliberately by setting up patent barriers and making a fence around their inventions.

Kiley: Well, there are all sorts of metaphors. Currently, there's something the Japanese are accused of called patent flooding. Someone in the States or elsewhere will make a seminal invention--some would say because people outside Japan are better than people inside Japan at breakthrough innovation. The Japanese will respond by imagining all the things that could be done with this [invention] and flooding the system with patent applications to the point where they've got to be dealt with in respect of the first patent.

The Patent Prosecution Process

Working with Scientists

Hughes: Well, shifting topics: I assume when you first began to deal with Genentech scientists that they knew very little about the patenting and licensing process. What did you do, assuming you did, to bring them up to speed? And were there resistances?

Kiley: [pause] I would say that the less you know about molecular biology, the more likely you are to encounter resistance when you want to talk to a molecular biologist. Because they want to talk about things of interest to them, not the basics that they've gone through decades ago in their postdoctoral studies. Well, you have to talk about basics, if you're going to bring someone up a learning curve. The nice thing about molecular biology is one can picture in one's mind what's going on. These are little machines, libraries, and railroad cars running down the tracks, and instead of smoke, RNA is coming off. So you can quickly get an intuitive grasp of how this stuff works.

Hughes: Were you getting a grasp mainly by talking to the scientists?

Kiley: Yes. I think scientists write for other scientists, and if a lay person wants to get an understanding, he's better off talking to the scientist and getting it described in the terms scientists must use when they're talking to nonscientists. The problem with the scientific literature, as I view it, is it is written in a sort of dry lexicography that lacks emotion, lacks excitement, makes everything seem straightforward and easy after the fact. People never write about their failures. They never write about the dry holes they have drilled or the blind alleys they've gone down, and so you can't read the scientific literature and understand whether something was patentable or not. You have to dig in further to find out why it was hard. At the end of the day, nature is logical. Everything makes sense when the underlying mechanisms are understood.

But patent lawyers, particularly when they're advocates to judges, have to have the ability to lift their audience out of their shoes and plant them back in time when many things were unknown and many things that proved not to be true were known and so everyone was awash in a sea of ignorance, and now ask whether something that broke through all that to the good of humanity is deserving of a patent. Was it obvious or not? Well, to learn how to build that kind of a case, you need to talk to scientists. I think it helps to have come from a trial background because you had better learned how to collect what ultimately will be deployed, not only in the Patent Office but in the courts.

Hughes: Did you find much concern amongst the scientists early on about what patenting might do to information flow?

Kiley: The people who came to Genentech in the early days had already overcome concerns they might have had about the baleful effects of corporate employment, patent attorneys, and all that sort of thing. Those issues were more often aired in academic quarters by such people as questioned the Boyer-Cohen patent at Asilomar and so on. But having said all that, it was nonetheless very clear delay in publication would not be tolerated because that might lead to a

scientist being scooped. Obviously, some scientists were more interested in talking to patent attorneys than others. I never had anyone succeed in refusing to talk to me when it was commercially important that he do so.

Hughes: But you had to be insistent in some cases?

Kiley: Oh, not really. The hardest thing was to get people to take time away from the preparation of a manuscript to answer the kinds of questions the manuscript then under furious preparation would not answer. But people could always be found to help you do that. It's just part of the job.

Scientific Publication

Hughes: How easy or difficult did you find it to adjust what you needed to do in terms of the patenting process with what the scientists needed to do in terms of publication?

Kiley: [pause] On the one hand advantages could be imagined to deferring publication until some additional science could be done, the better to justify patent claims of a particular breadth, in order to be sure you knew where the N-terminus of the molecule was, and so on and so forth. There is also a danger in deferring publication that I have seen manifest on several occasions. So for example, Genentech deferred the tPA publication for a period of months. In the event, it was asserted by Genetics Institute the tPA cloning effort did not arise to patentability, rather that that cloning was within the skill of an ordinary worker, witness the fact that Genetics Institute had succeeded in getting a clone of its own, assertedly before coming aware of our sequence through publication. It was clear we had done it first. Their assertion was yes, but they were able to do it too, and therefore it's obvious how to do it, and we shouldn't be entitled to a patent.

Subsequently at Geron we, working with our collaborators, succeeded in cloning the gene for human telomerase, and the question arose how long we should defer publication of that sequence. My answer was, "Publish it as fast as you possibly can," having learned from the tPA experience. And that was done, and we are happy that it was done because within days or weeks of our publication, others were announcing they had done so as well. And it is now open for us to say the competing work was not original work.

Enablement

Hughes: Is a disclosure enough for one skilled in the art to actually practice the invention successfully?

Kiley: Well, that is obligate in the law if the public is to have fair exchange for the limited period of monopoly a patent provides. Having said that, one needs to distinguish between at least two cases. The first case is, have you described the science you have actually performed hands on in such a way that it can be replicated by another without undue experimentation? And the

answer to that should be yes. Then the next question is, to compare the quantum of teaching in the patent text to the breadth of things encompassed by the words of the patent claim. And there the question is, have you said enough in the text of your application that, taken with what we expect workers in this area to know without reference to your patent, a number of things could be made using your technology that is roughly commensurate with the breadth of your claims. Or have you asked for a much bigger monopoly from the patent system than you have given back to the public things truly obtainable by it without undue experimentation? And that's where all the fight comes, because people on the basis of skinny science often claim to have covered the landscape.

Hughes: Shouldn't that judgment properly be made by the patent examiner?

Kiley: Certainly, and for a long time in biotechnology it's fair to say patent examiners more often than not were resolving those questions generously toward applicants. It's only recently one begins to hear that the pendulum is being pushed in the other direction by the Patent Office and by the examiners. But it's very difficult for a patent examiner, without more investigation than the Patent Office budget or procedures permit, to get a real sense of how far scientists can run with the hard science described in a patent. And one often sees, in biotechnology patents in particular, page-upon-page descriptions that come right out of the patent attorney's form book of what one does to extend the science in this, that, and the other direction.

Hughes: It seems to me an extremely problematic area. The tacit knowledge--the practical experience of those who have actually practiced the technology--doesn't necessarily get included in the disclosure. Students go to laboratories to get hands-on practice in specific technologies because in many cases you can't fully get it from written descriptions.

Kiley: Well, the notion is these [disclosures] are read by grown-up scientists and that you don't have to teach them how to suck eggs.

Hughes: But, as you mentioned, novelty is one of the criteria for patenting, so there has got to be something new about the invention.

Kiley: Well, novelty is easy. It's easy to look at two things and decide whether they're the same or different. All of the trouble starts when the question is not whether it's new, but whether it is sufficiently beyond the reach of a person of ordinary skill that it is an accomplishment extraordinary enough to merit the grant of a patent. That is a very metaphysical question. And that's where all the fur flies in litigation, aside from the question, is the claim broader than it ought to be given what's been learned by the public from a reading of the patent. Or is it, as the trial court said in the tPA litigation in Great Britain, "greedy and overreaching."

Changes in the Patenting Landscape in Biotechnology

Hughes: My original question was, how did you go about patenting at Genentech?

Kiley: Well, may I say that I encounter the Genentech patent group from time to time these days, and it is so infinitely more sophisticated than ever I was in the early days, that I find it remarkable Genentech even survived on my watch.

Hughes: Well, everyone else was a few steps behind Thomas Kiley, I'm reckoning. What has changed?

Kiley: To a certain extent, in the earliest days the road ahead of us was clear because we were leading the pack. Now, everyone's eating everyone else's dust and there's just a lot more dust in the patent atmosphere than there was in the halcyon days of the industry's youth. Secondly, to the extent we were regarded as first or among the first, people wanted to talk to us. Now, if you're a biotechnology company, you are one of thousands, and it's a lot more difficult to get your signal heard over the noise everyone else is making and over everyone else's clamor for the support of corporate partners, so things are more difficult from that standpoint.

Thirdly, the technology has grown much more multifarious and complex. So there are many kinds of patent questions one deals with now that one didn't have to deal with in the earliest days. To an extent, the action has moved back towards small molecules, as the known proteins of therapeutic value have been picked off the lowest limbs of the opportunity tree. So there are all sorts of new questions about practices in claiming organic molecules, and the limitations of predictability in respect of those. You've got all of the issues arising from the patenting of genetic sequence and assignment of function to it. And in many respects your competitors, if they're biotechnology companies, now are big enough to put up a bruising fight. At the same time, big pharma companies have gotten bigger through consolidation, so in some respects it's become a bit of an elephant dance.

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Kiley: Genentech is no longer a mouse, but then again, it isn't the biggest pharmaceutical company in the world. Life can be very complicated if you're a brand new biotechnology company of mouse-like or murine proportions.

Looking Back at Early Patent Prosecution at Genentech

Hughes: Were Genentech patents to any extent looked at as prototypes of what others might seek to model in biotechnology?

Kiley: I honestly don't know. It would be unusual if someone at some point hadn't looked at them as aids in the preparation of his or her own. I would say as time has gone by and the science has become richer and the law has begun to be announced by appellate courts, people are probably doing a better job than one was able to do in the earliest days. But the patent law is forgiving in that respect. It recognizes through such things as the so-called Doctrine of Equivalents that people in breakthrough technologies, out of necessity making up their vocabulary as they go along, are entitled to a certain degree of sympathy and flexibility in interpretation.

Hughes: Looking back, as I presume you must have done, at some of those early patents that you wrote before the last one in 1980, were there things that now you would state differently?

Kiley: If there were, I would never be permitted to admit that.

Hughes: Oh, all right.

Kiley: Now, if you read the *Wall Street Journal*, and are then asked if you had the *Wall Street Journal* yesterday that you're holding in your hands now, would you have invested differently? Obviously, one can find instances where he or she would have.

Hughes: Were you in general confident that what you were doing was going to stand up and be useful and achieve what you and Genentech wanted it to achieve?

Kiley: Dealing in what [Justice] Frankfurter called a metaphysical branch of the law, one can never be absolutely confident anything he does will withstand scrutiny of the kind accorded patents in hard-fought litigation. Somebody has made something that by definition is new and exciting and he is in a hurry to publish it. You've got to write it down and get it so right in a matter of days or weeks that as long as twenty years later judges with all the time in the world, educated by experts in the field with the benefit of twenty years of hindsight, and lawyers able to spend all the money in the world because something has suddenly become very, very valuable, and have them find no fault in it. It's a daunting proposition, but it's something patent attorneys do every day and hope they do well enough to withstand the challenge.

Hughes: I take your point: there's no certainty in this world about much of anything and you do your best. Yet you were moving into a field that was even more uncertain than most areas of human endeavor, and the rules weren't clear. Or were they?

Kiley: [sigh] Well, it certainly wasn't clear to me what things would be best to do. I can't say it was clear to any of us what the whole field of choice was on the menu of things that might be done. You just tried to do the best you could in real time and move onto the next task.

I remember saying to my pals at Genentech during one of our annual planning sessions I didn't think it was terribly important that we knew everything we were going to be doing five years from now. Only important that we surround ourselves with people smart enough to figure it out as we went along. If you're expected to know today all the things you need to know in the next five years, then what's the point of the company paying you salary tomorrow and for the rest of those five years, because you're got all the answers today?

Hughes: So to an extent, you were flying by the seat of your pants.

Kiley: All entrepreneurs do. You try to diminish the uncertainty as much as you can, but at the same time, I have had to let people go who were so risk-averse that they would neither fish nor cut bait. They wouldn't complete a task until all the risk was out of it, and time doesn't permit. Even Henry Kissinger used to make diplomatic agreements he knew were not air-tight, but he accepted a certain amount of uncertainty to get them done in real time. He'd sweep the rest under the rug in what he called the "language of constructive ambiguity." One tries to build no constructive ambiguity into a patent or a contract, but sometimes it ends up there anyway, because the thing has to get done.

More on Genentech in the Early Days

Assessing the Company for Investment

Hughes: What place did patent position hold in those early days when investors were looking at Genentech, probably very unsure about how to evaluate the science? Or let me put it more open-endedly: what did investors look at?

Kiley: Well, it's very clear that the patent was a check-off on their due diligence list. But clearly they were looking at people and opportunity. What is the market opportunity? Are these people that are capable of realizing the opportunity? What returns can be expected?

Now, to analyze the opportunity, one had to look first and foremost in the earliest days at the science, the molecular biologists, and the ancillary sciences that served the molecular biologists, who then ruled the roost. Nowadays, when there are molecular biologists in all sorts of companies, you have to look at much more. You have to look at the company's ability to take the science--let's assume that it's quality science--but everybody's got quality of science--can they take it the next step? Can they take it into the clinic? Do they have the capability to choose the right path?

Now, in the early days of Genentech, neither it nor other companies like it were competing on the basis of clinical expertise. Our first step up the ladder toward FIPCO, past the science, was to prove we could make these products in pilot- plant scale, and then prove that we could make them in industrial scale. So we differentiated ourselves from other companies, first by industrializing gene-splicing--and by that I mean taking it out of the university and into a company--and then by engineering the technology so that we could move from the bench to the bottle. Indeed, there was a time when you couldn't get a publication out of Genentech that didn't have little bottles all over it and indented into it to make the point we were moving from the bench to the factory. Well, now lots of people can make recombinant proteins in large scale, so you have to compete on the basis of your ability to take them into the clinic. And that [takes] skill and financial resources.

Road Shows

Hughes: Were you part of some of the early road shows?

Kiley: I did not attend the road shows associated with the public offering or any of the secondary offerings. I did get on the road, as many others did, to market the R&D limited partnerships we used as one means of financing the clinical trial. And because I hate to ask people for money, I couldn't figure out any better way to sell those than to buy several of them myself, and then stand up and tell people I'd put my own money into them--which turned out to be a very good thing to do indeed.

I do recall and will always chuckle about two things I was told about the road shows associated with the public offering. First, that Fred Middleton, then chief financial officer at Genentech, had done a wonderful job in getting the process underway and the bankers in tow and events in train and running around the United States with others on the road show, making presentations. But first they had to take the presentation off Broadway, if you will; they would go to Europe. And Fred showed up in a first-class lounge at San Francisco International Airport with various dignitaries and senior members of Genentech management, toasting the imminent success of the IPO, and then they went to board the plane, and Fred learned his passport had expired! And as the plane winged off into the sunset, I have a picture of Fred trudging out of the airport, bags in hand. [laughs] Happily, I got his passport renewed in time for him to join them, having missed only one stop.

The other thing I remember hearing was Boyer calling in from Europe, telling how grueling the pace was, how hard he was working, pointing out the private jet that they were using to fly from some castle to some other watering place just that evening hit a little turbulence and spilled an entire tray of caviar over his knees. [laughter]

Hughes: That was certainly tough.

Process Patents and Foreign Infringement

Hughes: Well, could we wind up with a few questions I picked from reading your papers?

Kiley: Sure.

Hughes: In your presentation to a subcommittee of the House of Representatives in February 1986, you argued for, quote, "meaningful process patents." Can you recall what was behind that comment?

Kiley: I believe this had reference to a conundrum Genentech faced, Amgen faced, and other [biotech] companies faced that were making products available for the first time in copious quantities, sufficient to serve the market, but which were old in the sense that they had been known previously as compositions of matter and so could not be patented as compositions. Erythropoietin is one such example.

And so suppose you showed the world how to make a microorganism that produces, or a cell that produces, large quantities of erythropoietin, and you have a patent on that in the United States? Now, may not someone lie off your shores and produce erythropoietin beyond the territorial reach of the American patent on the EPO-producing microorganism, and with impunity ship that product into the United States and compete with you?

The United States has evolved proceedings under the International Trade Commission in Washington that give an inventor relief in circumstances akin to that, where the patent he's got is a process patent--that is, a patent on a method for doing something or making something. If the foreign competitor is practicing a process which, but for the fact that it's beyond the

geographic reach of the American patent, would infringe the American patent--well, there was a problem with that.

This is getting more specialized than the readers will appreciate, but there was a case called *In Re Durden*, in which the American patent court construed process patent law in a certain way. Until then it had been thought a process, which is a series of steps, could be patented even though the particular steps were not new, if they were being practiced on, for example, a chemical previously unknown. So the step of oxidizing A to get B is old, but if A was never known, so that B is a new product, then you ought to be able to patent that process. "No, you may not, said *Durden*," because, without reference to the subject on which you're operating, the process steps themselves are old.

Okay, now Amgen has a problem: its patent on the microorganism does not extend to prevent overseas competition, even though the competition is aimed at the American market. And *In Re Durden* says Amgen cannot have a patent on a method of producing erythropoietin which comprises turning on a bug that's been engineered to make it, and collecting it, because that process is old with reference to polypeptides generally, whether or not anyone has ever done it before for erythropoietin. So it's a catch-22 for Amgen: it can't have a patent on a composition, because the composition was old; its patent on the bug won't prevent Chugai, in this case, from shipping erythropoietin into the United States, and under the *In Re Durden* interpretation of the process patent laws, it can't have a process patent either.

So at the end of the day, having made available to the world the boon that is erythropoietin, Amgen will have no revenue. That was the subject of a lot of Genentech testimony before various committees and subcommittees of the House and Senate, and a lot of Amgen testimony as well, and of a International Trade Commission proceeding that ended adversely, I seem to recall, to Amgen, because it was obliged to try to describe the microorganism as if it were a process, to fit itself onto the Procrustean bed of the ITC laws as they then stood. Ultimately we got a hearing in Washington. I remember sitting in Boyden Gray's office [Counsel to the Vice President] in the Executive Office Building, pitching this and being impressed that he had three fireplaces in his office.

Ultimately, the law changed to permit relief in those circumstances. But it was a statutory change that had to be made, and [was] opposed, as all patent legislation is opposed, by Sidney Wolfe and the enemies of the pharmaceutical industry and the American Association for the Advancement of Retired Persons and so on. One thing that makes it difficult to fix problems in patent law as it affects pharmaceuticals is, to the extent [legislation] strengthens pharmaceutical patents, people will be found to oppose the fix because of the prospect it makes medicine more expensive. As you know, we're seeing that in spades in the current presidential election. And so every time you manage to fix something statutorily, you pay a price for it by giving elsewhere on other law. But then again, that's compromise.

The Changing Value of Patents

Hughes: Here is another quote from Thomas Kiley, this time from a talk to the Bay Area Business Development Round Table in 1990: "In the beginning, patents matter some. In the middle, they don't matter much. In the end, they matter a lot?[1] Would you care to explain?

Kiley: [laughs] Sure. You can't raise venture capital unless you can check off the patent box on the checklist of the VC who's doing due diligence. No one will invest in the development of technology that can't be protected, so you need a patent story. Okay, but then in the middle, everyone's got a patent story. By definition they wouldn't exist if they didn't have one. So now investors seeking to choose amongst companies for investment see everyone saying: "We have patents. Sure, we've got patent applications. Yes, we'll be protected." And so the availability of a patent story as a criterion for choosing amongst companies is blurred. Beyond that, everyone has patents. They issue, in part because the Patent Office, through many of these years, was quite generous in handing them out. And indeed, the patents overlap because of the nature of the enterprise by which science gets done in biology. Journey of a thousand miles, filled with many steps, all with patents--everybody's got a patent story. Well, in the end, if companies contend over something that has turned out in the meantime to be very valuable, then a lot of this underbrush is burned away, you go through the refining fire of litigation, if you will, and finally you get an answer, because courts are in the business of giving simple answers to complex questions.

The simple answer we'll get from the courts in respect of the [Gore-Bush] presidential election ultimately will be, he wins; he loses, or words that will cause that effect. But the issues are complex. Well, so too, patent litigation. Complex issues get aired--issues of law, issues of fact, issues of science. But in the end, either your patent is valid and infringed or it's not. Those are black and white outcomes, and they can bite deeply.

If you are suing on a patent, and you lose, all right; you had a patent, you were looking for a patent when you got that one, but your business is still there. You may have to tolerate some competition. On the other hand, If you are defending against a patent, and the patent is held valid, all you need do is leave the business and practice some other form of business. But what if that's your only business? Then you're out of business. So in the end, you may get it in the end, when the court is dealing thunderbolts.

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[1]"Patents in the Beginning and in the Middle and at the End," draft, November 13, 1990. (Kiley papers, unprocessed, The Bancroft Library.)

V GENENTECH LEGAL COUNSEL, 1980-1988

[Interview 4: January 3, 2001] ##

Intellectual Property Issues at Genentech

The Interferons

Hughes: Please talk about the interferons, one of the early Genentech products.

Kiley: Well, interferons fall into two broad categories, one of which has subparts. Genentech first proposed to clone what are called alpha and beta interferons or, as they were then known, leucocyte and fibroblast interferons. We entered into a negotiation with Hoffmann-La Roche of Nutley, New Jersey, looking for funding for that project. The other interferon I'll come to later is gamma interferon, that falls into a whole different category of activity.

Our negotiation with Roche on the interferon front lasted over the course of near eighteen months. Principal participants were myself, Bob Byrnes, and, coming in and out of the process, Bob Swanson. I don't think the people at Roche had ever encountered anyone quite like those from Genentech. They regarded us as rather presumptuous in our demands, considering that they were representatives of a major pharmaceutical company and we were, as Ellis Anderson, their general counsel and vice president for administration, said, "mere entrepreneurs."

Ultimately, what it took to get the deal done was a visit to Genentech by Bob Clark, who was then the CEO of Hoffmann-La Roche and whom I regarded as wanting a Genentech deal with interferon to be the capstone of his career. He was approaching retirement. I had gone to Basel just a month earlier, in latter December of 1979 to conclude in two days a negotiation with Roche Basel, on behalf of a different client altogether. I remember having been told by Bob Swanson's secretary in the wake of my trip to Basel, she'd received a call from Bob Clark who said he was going to fly out with his colleagues in earliest January and wasn't going to leave until we'd completed our interferon deal. "Would," he said, "the peripatetic Mr. Kiley please make himself available at that meeting as well." This was before I'd joined Genentech as a full-time employee.

So Mr. Clark flew into town early in January of 1980, participated in a day-long meeting attended by Genentech representatives, his colleagues (including Mr. Anderson and others), and Tom Perkins. He agreed in the course of that day to double the sums payable to Genentech

by way of front money and milestone payments. Then just before going off to be wined and dined by Mr. Perkins, he turned archly to Ellis Anderson and another of his colleagues and instructed them to fly down to my office in Los Angeles and write up the deal and not return to New Jersey until the deal had been done and signed by Mr. Anderson--which put him rather in a difficult spot. That was done.

Interferon at this time was a very hot topic. Many believed it held out the potential to be a broad-spectrum agent against cancer, though its mechanism of action was poorly understood. Just days after we signed the arrangement with Roche, Biogen made a big splash in the international press by announcing it had cloned alpha interferon. Had that announcement come just a week sooner, I doubt very much we would have made our deal with Roche. And, who knows, perhaps years later the Roche relationship would not have evolved into its ownership of the controlling stake in Genentech.

It developed Biogen had not in fact cloned alpha interferon itself, but rather a DNA which included alpha interferon and various additional sequences at the N- and C-termini of the structural gene itself. But on the basis of that work, they filed a patent application, which came to our attention when it was published abroad, that purported to claim that sequence and any other sequence that hybridized to it. So on the basis of what we regarded incomplete work, they attempted to dominate the whole field of alpha interferon and anything remotely like it--something the British court in our later tPA case would call in a different context, "greedy and overreaching."

Our collaboration with Roche went forward. We were teamed with Sid Pestka at the Roche Institute. In July we succeeded, with the aid of some RNA source material Dr. Pestka provided, in cloning not just one alpha interferon but a whole series of them. It turned out the alpha interferons were a family, and we, I think, were the first to recognize that, and the first to clone a sufficient number of them to justify a patent claim purporting to be on the whole family.

Now, the earlier work of Biogen precluded us from writing such a claim unless we could make sure everything contained within it was different from what Biogen had done. I decided to claim not simply a substance containing an interferon sequence, but rather an interferon sequence capable of expressing mature alpha interferon, that is, the very thing. And so in July of 1980 we filed the patent application on the alpha interferons, identifying Goeddel and Pestka and perhaps one other as co-inventors.

I may say our interest in alpha interferon and the validation of our perceived capability in that area the Roche deal represented did not hurt at all in setting the company up for its initial public offering in October of 1980.

Well, as inevitably happens when rival claimants file applications, the Genentech and Biogen patent applications were put into interference proceedings in the United States. This is a proceeding in which the Patent Office and ultimately the Patent Office Board of Interferences determines which of two or more rival claimants to a single invention are entitled to priority. That is, "Who was the first inventor." Along the way, Roche and Schering, which latter had licensed Biogen's patent rights in alpha interferon, made a deal under which each would license the patent properties of the other while the interference proceeding went forward, the notion being that in the countervailing royalty payment scheme in this cross-license, the party winning

the interference would get a greater reward. And that was done. Ultimately, following my departure from Genentech, I believe Genentech prevailed in the interference and so was recognized as entitled to very significant patent protection for its work in the alpha interferon field.

Beta interferon, or fibroblast interferon as we then referred to it, was also the subject of the Roche-Genentech arrangement. David Goeddel succeeded in cloning fibroblast interferon as well, as did a number of other workers elsewhere in the world, chief among them, a young scientist in Japan by the name of Taniguchi, later a full professor at Tokyo University. And I don't know that I can say how ultimately that shook out, although reasonable men might differ whether in the ultimate event Genentech was the first or merely the second to clone fibroblast interferon.

Subsequently Genentech pursued what was regarded then as the holy grail of the interferons, something called immune interferon or gamma interferon. And as it had done in the Roche case, Genentech sought corporate sponsorship for that project as well. Indeed, for a time, gamma interferon had figured in the Roche negotiations, but we had extracted it from the subject of that arrangement on the notion Roche wasn't paying enough to entitle itself to all the interferons.

Gamma interferon is probably a misnomer. Its properties are very different from the other interferons. We first entered into an arrangement with Daiichi Seiyaku of Japan, then I think Japan's sixth leading pharmaceutical company, who, remarkably for a Japanese company, were willing to commence funding the work solely on their perception that Genentech had the best chance to pull it off, of any of the contestants.

Hughes: Why is that unusual?

Kiley: Well, because an investment of that kind involves substantial risk. We had nothing in hand other than ambition, and Japanese pharmaceutical executives tend to be rather risk-averse because of the career-threatening prospects of failure. But Keitaro, known affectionately as "Dick," Yoshida of Daiichi, had faith in us and sponsored that project. Ultimately, we were able to add Boehringer-Ingelheim of Germany as another sponsor, each in exchange for product rights in their respective territories.

In or about May of 1982, I learned by telephone while at a Silverado company retreat that David Goeddel had succeeded in cloning gamma interferon. Gamma interferon proved a disappointment to our partners abroad, and for the longest time was a product searching for an indication against which it could be used. Genentech got it approved for chronic granulatomous disease, an orphan market, and later licensed it to Connetics Corporation, of which I'm a director, which in turn spun it out into a company called Intermune. In the meantime, by coincidence, some European workers published a double-blind study in which they appear to have demonstrated rather convincingly that the product is good for the treatment of pulmonary fibrosis, a huge market. On the strength of that, Intermune has succeeded in becoming a public company and quite a valuable one.

Hughes: Did either of the other interferons result in any sizeable product for Genentech?

Kiley: Schering-Plough proved better than Roche or Genentech at making something of the interferons. And I think alpha interferon has found some application in the treatment of hepatitis, whereas beta interferon in the hands of Schering-Plough and Roche has yielded a product that has had some very good activity against multiple sclerosis. But it's ironic that Genentech, at least in the alpha interferon case, and vis-à- vis Biogen in the beta interferon case, appears to have won the cloning race only to lose the commercial race.

The Riggs-Itakura Patent

Hughes: I've read that the Riggs-Itakura patent is highly significant amongst the early biotech patents. Would you tell me about that, please?

Kiley: There are a series of patents that have issued under the Riggs-Itakura rubric, all stemming from the first science Genentech ever did, that being the somatostatin project Genentech funded at the City of Hope and the University of California at San Francisco. The several patent applications resulting from that work, some of them authored by me, certainly claimed broadly in terms the notion of producing a heterologous protein under what I called homologous control. That is, under control of regulatory regions ordinarily associated with microbes, one produces, a non-microbial protein. By our lights, that had never been done before, and ultimately I think we persuaded the Patent Office we were entitled to claims more or less of that scope.

The broad claims of these patent applications, as they were in the late seventies and early eighties, certainly facilitated our entering into the kinds of corporate alliances or partnerships we needed to bootstrap the company. They gave us, at least as viewed then, a colorable path to dominating the foreseeable applications of gene-splicing in industrial settings, more or less akin to the way the Boyer-Cohen patent was perceived. And indeed, in entering into arrangements with such as Lilly for insulin, Kabi Vitrum for growth hormone, Roche for several of the interferons, the right to practice under these patent rights was part and parcel of the whole arrangement.

I'd rather not comment on how the Riggs-Itakura patents have fared in litigation, largely because I'm not confident I'm acquainted with all the detail of that, although I have been told a federal judge in at least one contest in the United States has construed key claims of the patent in an unrealistically narrow way. The corresponding patents were the subject of some litigation or revocation proceedings in the United Kingdom, brought by Lilly itself. Because even though the claims purported to protect the insulin markets licensed to Lilly, Lilly found them troublesome from the standpoint of Lilly's wish to use recombinant DNA in fields other than those licensed from Genentech.

Genentech ultimately decided to make licenses available under these patents here and elsewhere in the world on a non-exclusive basis for a relatively modest royalty, more or less as had been done by Stanford in the Boyer-Cohen case, with the exception that Genentech held to itself, for obvious reasons, rights in fields it had earlier licensed to others, like insulin in the Lilly case, and reserved the right to abstract from the broad field available to license other things it intended to undertake.

Hughes: What was the rationale behind Genentech's ostensibly charitable approach?

Kiley: Well, it's fair to call it charitable, in one sense, because the revenues from licensing were demarked for a Genentech institute to promote education in molecular biology. But in another sense, I think it was a matter of a surfeit of riches. Genentech had more patent protection than it could fully exploit. Why should it play dog in the manger with its patents and use them to prevent others from doing things Genentech itself could not do? Patents are principally of use in protecting the markets a company has decided to serve itself. But there was never during my time at Genentech a lot of enthusiasm for running around suing people merely to recover royalty income. That's not what we've thought patents were principally for.

Hughes: Yet Genentech has a reputation, beginning way back, of putting a lot of stock in a strong patent position and certainly was never considered as a pushover in the field.

Kiley: In the pharmaceutical business in the time in which Genentech first found its legs, pushovers got pushed over. And that's simply life in the real world. So no, we didn't advertise ourselves as pushovers. In fact, we made as much bluster over our patent rights as we thought appropriate, short of the kind of saber rattling that can land you in district court where someone says, under the Declaratory Judgment Act, he's not obliged to live under a Damoclean Sword. If there's a justiciable controversy he can call you into court and ask the court for an adjudication of the validity of your patents. Well, those are things one likes to be in control of--when, where, concerning what subject, and so on. So there's a rather fine line all intellectual property executives walk, and that is to be credible in your determination to enforce your rights, but on the other hand, not to pull triggers prematurely, leading to unwanted and perhaps unwarranted litigation.

Hughes: Did the industry, anticipating the issuance of the Riggs-Itakura patent, worrying about it in a way that people in the know worried about the terms in licensing Cohen-Boyer?

Kiley: I don't know. I can't say anyone ever came up to me at a conference and said, "I'm shaking in my boots over the prospect that your patent's issuing."

Hughes: [laughs] But there could have been discussions in industry newsletters, for example.

Kiley: Well, perhaps there was. I don't recall. I knew that it was bruited about that Genentech had filed some very broad patent claims, and I recall seeing some press clippings when they began to issue, analogizing them to the Boyer-Cohen patents in some respects. But everyone was filing patent applications. You know the old military saying, "If it moves, salute it; and if it doesn't, paint it." Well, people were painting "patent pending" on everything in the molecular biology landscape every day, and no one really was willing to predict what the Patent Office might ultimately make of all these things. They were inchoate until they issued in patent form. By the time many of them did, companies that might have been cowed earlier had assumed some substance and could take a businesslike approach to dealing with them.

Patenting and Licensing Strategies

Hughes: Genentech could only do so much. Was there a notion that what it couldn't do, it should hand over to another company because ultimately the success of the industry depended on the success of more than one company?

Kiley: Well, I should say that I was otherwise occupied when the licensing scheme under these patents was hatched, and so all I know of it is really hearsay. I've drawn some inferences about it I'm happy to share. I don't think Genentech was at all acting like a charitable organization. It was doing what it thought made sense with such assets as it had. And if you've got these patents, and some revenue can be gleaned from them that can be put to a good purpose, why not? At the same time, where your vital business interests are not directly at stake because people are seeking licenses for things you don't wish to pursue, there's very little motivation in chasing them around the landscape, threatening them with patent litigation. And you've got to accept a relatively modest royalty to gain a significant number of licensees, without a lot of histrionics. At a time when Genentech was focused, as it should be even in the present times, on the things it regards as most important to its growth, one doesn't want to divert a lot of management attention or business development personnel to these sorts of secondary and tertiary objectives.

Hughes: Address the possibility that people such as Swanson and yourself were thinking in larger-than-Genentech terms, striving to get this industry off the ground and noticed and money flowing into it.

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Kiley: Well, let's deconstruct that. First, everybody at Genentech basked in the glow of doing things we thought would be good for sick people and helping create an industry that could lead to better health and the prevention or amelioration of disease. We thought we needed the protection of patents in order to justify investment in our company, in order to return margins that could permit us to reinvest in doing what we thought we could do perhaps as well as anyone else in the world at that time. So in a sense, maximizing profit is a way of maximizing your impact on disease. We weren't disposed to give anything away, because to do so affects our ability to do those other things. Indeed, in all candor, if our focus had been more on building an industry than looking after our shareholders, I don't think we would have asked Niels Reimers for an exclusive license under the Boyer-Cohen patent to all mammalian polypeptides.

Obviously, trade organizations exist for the good of the industry at large. And it's certainly right in some subjects that what's good for the industry is good for any individual company in it. But that doesn't mean any company is run like a member of commune.

Hughes: In the same article in which I gleaned some information about Riggs-Itakura, Mr. Kiley was quoted as saying, "There are two kinds of patents--good ones and bad ones. Good ones are the ones I have."[1]

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[1]*Biotechnology Newswatch*, November 16, 1987.

Kiley: An obvious rhetorical flourish. Obviously, if others have patents that stand in the way of your doing what you wish to do, they're a problem. That's bad. If you have patents that permit you to raise investment and commit to research and give a good profit to your shareholders, that's good. Now, it doesn't mean there's any company in the world that has only perfectly valid and broad patents. Patents are legal instruments. Some are better deserved than others. In my opinion, the Patent Office is not a very effective filter against bad patents. At Genentech we didn't try to paper the walls with patents, but rather file those that we thought we were entitled to.

Hughes: Now who made the ultimate decision to apply for a patent?

Kiley: The company management did, on the recommendation of the law department, which at the outset was myself. We did very little prospective patenting. By and large, the patents I was involved in at Genentech were filed after the work was done, quite unlike a common practice today, which is to introduce a patent attorney to a wish and a prayer and then have him cook something up and purport to reduce it to practice constructively by the filing of a patent application. That seems to be the way the game is played these days, in many respects. If it is played that way at Genentech, it's beyond my ken.

Hughes: May we venture into the subject of trade secrecy? I have a quote from the prospectus for the IPO, which was October 14, 1980: "Although the Company has applied for numerous patents, it does not intend to rely solely on patent protection as the basis for protecting its proprietary technology. To the extent consistent with its policy of permitting its scientists to publish meritorious achievements in scientific journals and seminars, the Company likewise intends to rely upon trade secrets.[1]

Kiley: That is language that one finds commonly in prospectuses these days. Then, perhaps, it was somewhat uncommon for reference to be had to publication. We talked earlier about the importance of publication to Genentech's quality processes, recruitment, and so on, and of how important I and the other patent attorneys at Genentech felt it was to assure scientists the patent process would not unduly inhibit publication. Well, having said all that, it does not follow our doors were wide open for anyone who wanted to come through and collect scientific intelligence.

As a matter of fact, I remember vividly sitting with Bob Swanson in his office one day when a busload of Japanese scientists pulled up who had arranged a tour of Genentech's facilities. We watched them get off the bus and line up at the front door. Bob said to me, "How many Japanese got off the bus?" "Nineteen," I said. And he asked at the front desk, "How many cameras were turned in?" "Eighteen," they said. Whereupon the delegation was hunted down in the corridors of Genentech and the missing camera confiscated.

The most important piece of information that Genentech could secure at the bench in those days was the sequence of a particular DNA and perhaps possession of the physical substance, as well. With the sequence published, as it must be in a patent application, fishing out another copy of the gene from the common pool was a relatively trivial exercise. So we were obliged

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[1]"Genentech, Inc., Amendment No. 2 to Form S-1, Securities and Exchange Commission, Washington, D.C., October 14, 1980, p. 22.

to publish our most secret material in due course, but that left a whole universe of other things that typically were not published, but nevertheless valuable.

For example, until we began to ferment *E. coli* to produce valuable pharmaceutical proteins, all of the fermentation art had to do either with such things as making alcoholic beverages or antibiotics, small molecules of the kind that were largely secreted by host microorganisms and crystallized out of solution. Producing pharmaceutical proteins was quite another matter, and we were obliged largely to develop that technology for our own account. You couldn't find it in books, and it was not the sort of thing one published, but very valuable in terms of making these delicate proteins fully functional in large quantities and in an economic way.

Hughes: It was not published because it was considered scientifically mundane?

Kiley: It was not published because the process engineers that develop that technology do not come from a tradition of publication; do not crave peer recognition in the way bench scientists working in fundamental fields like chemistry and physics do, and because it's an accretion of little pieces of information that taken individually may not be particularly significant, but in the aggregate are very, very valuable.

For example, when we collaborated with Boehringer-Ingelheim in the tPA field, Boehringer-Ingelheim came to the plant Genentech had constructed for the purpose of recombinant production and basically lined off the plant and reproduced it more or less identically in Germany for similar purposes. So that sort of information, know-how as I would refer to it, needed to be protected.

Hughes: Were all the early biotech companies forced to develop their own fermentation technology, so it might vary slightly from company to company?

Kiley: I would say that's generally true. And indeed, once Genentech was no longer the only company in the world that was cloning and expressing things at a bench level, it differentiated itself in its releases by its ability to make things to pharmaceutical standards and put them in a bottle. And other people in their turn had to learn how to do that. So I found the whole trade secrecy thing to be useful in more than this secondary way. I found it useful to ensure that when we entered into arrangements with commercial sponsors like the Lilly's and Kabi's of the world, that when we reached for our chips at the end of the day we would get more than a manicure.

Fending Off Litigation from Licensees

Kiley: It was not unusual in the early days of biotechnology--I will say not unusual in the sixties and seventies--for companies who had licensed patents to turn and attack the validity of the patent when the stakes got high. And indeed, the Supreme Court of the United States said we needed to permit such attacks by the most economically interested party if we were to root out bad patents; that licensees who had turned on their licensors were acting like private attorneys general. Well, this in a day when patents were not regarded quite as bathed in holy water as they are presently and were prone to undoing by the courts.

So when we began to make arrangements with big companies, juggernauts like Lilly, we needed a way that would withstand scrutiny to ward off those kinds of attacks. If you forbade your licensee from attacking your patent, the courts would simply run right over it. And there were other putative ways of fending off attacks and assuring you got paid whether your patents were any good or not. But many of those amounted to patent misuse that might render your patents unenforceable through extension of monopoly, or broadening of monopoly or other things.

So it occurred to me we should not be licensing our patents, per se, but rather we should be selling microbial factories to people. We would build a factory and sell it to someone. They could use it for a term of years to produce what it was designed to produce and only that. To ensure that the microbial assembly line was not converted to "unlicensed" purposes, we would retain title of the factory until it was fully paid for, such that any unauthorized use of our property in our partner's hands would amount to embezzlement. And indeed, the contracts specifically put on our partner the burden of ensuring protection against embezzlement of the microorganisms.

Hughes: Was that a novel approach?

Kiley: It was.

The other thing we did, which was permitted at least during the time when we had only patent applications and no patents and at a time before the Supreme Court in *Chakrabarty* spoke and affirmed the availability of patents on new life forms, was we said we don't know if there are going to be any patents. And in the preamble to our arrangements our partners recognized that uncertainty and in doing so forswore any later attempt to say our patents had coerced them into agreeing to pay royalty on unpatented things. And so we avoided what's called a tying violation under the patent antitrust laws, in which you use a patent to extract a royalty from some unpatented article of commerce. All we asked of our licensees was to pay for the factory. Since they acknowledged one couldn't determine the value of the factory except over time as it produced its intended subjects, the installment payments were set as a royalty, percentage payment on things that were sold out of the factory. After they'd done that for twenty years they could own the factory and use it for any purpose they wished.

So we gave them an amalgam of things. The amalgam constituted inchoate patent rights and unpatented know-how and tangible biological materials. The parties recognized their inability to apportion value amongst these several objects, and so in effect agreed to pay on any use of the factory, whether or not the trade secrets became public or whether or not the patents issued. In doing so, they shook hands with the Genentech tar baby in a way that made them inextricably bound to fulfill their royalty obligations, irrespective what happened to the patents, and so they were disincented from attacking such patents as issued. I think it was a matter of great frustration to Eli Lilly through its whole litigation with Genentech that it was wrapped in this web of admissions and contractual undertakings.

Now, in terms of know-how over time, it was our practice in the earliest days, those I remember most clearly, to tell our partners that they were free to practice without regard to our patents. And that was true as to any patents issuing during the term of the royalty obligation. So they had access not only to what we had at hand at any given time, but also to such

improvements as might be made within the defined period. Likewise, we had some obligations to deliver future know-how, although those were not unlimited in time.

Hughes: How did the transfer of know-how actually happen?

Kiley: I think an awful lot of it involves people exchanges--people working in a Genentech manufactory or sending people there, along with transfer of voluminous written information as well. In this business, submissions to regulatory authorities are usually the first place you'd go to find out most of what you need to know about any given product--how it's made, how it's purified, how it's packaged, and so on and so forth.

Hughes: Since you've said that trade secrets were part of the intellectual property of Genentech, wouldn't some form of control over the information being generated in the company have to be quickly imposed, particularly considering that many scientists in those early days came from academia where freedom of speech was the norm?

Kiley: Employees signed garden variety confidentiality agreements even in the earliest days. But possessing those agreements and enforcing them are two different subjects. We wanted our scientists to be part of a larger community of science made up of collaborators and other sources of information. It turns out if you go to a scientific conference, sometimes the least part of what you learn is what you hear in the presentation; rather it's the exchange of information that takes place in rather a collegial way. And the culture of science is simply that you can't get without giving. You're not going to be told very much if you're not reciprocating in some way. Whether it's ever been spoken or not, I think a sensible practice is to rely on employees' best judgment and hope that they're just a little bit better at extracting information than they are at doling it out. Information is currency. Collaboration was king at Genentech. You can't collaborate if you're not willing to share information.

Academic Freedoms at Genentech

Hughes: I've heard that the culture of early biotechnology companies was modeled after the academic pattern.

Kiley: I think that's generally right. The advent of biotechnology was influenced by the influx into the industry of people of an academic bent, coming from a tradition of publication in their particular fields. Prior to that time, the pharmaceutical industry was rather hidebound about secrecy. I think our ability to differentiate ourselves from the major [pharmaceutical] companies was an important element of our ability to compete for the leading lights in molecular biology. We obviously had other advantages as well. Herb Boyer in particular should be given credit for ensuring that cultural shift took place as we moved from the classic pharmaceutical industry into the new biotechnology. I think that it's worked for the industry.

Now, I came to Genentech from a very narrow perspective. Not only an intellectual property lawyer, but an intellectual property trial lawyer. So most of what I saw about trade secrecy was in the arena, if you will, where you were dealing with a *fait accompli*--theft. You

were pursuing someone. And never as a trial lawyer was I obliged to regard information as fugitive on the one hand and sometimes desirably so on the other.

Hughes: What did that mean when you started practicing at Genentech?

Kiley: Oh, it probably means that for a time I acted like a pencil-necked suit until the scientists were able to educate me sufficiently. Actually I've got a size seventeen neck now.

Hughes: [laughs] In practicality, Genentech and other biotech companies were unlikely to be able to entice outstanding molecular biologists to come to the company unless they received the appurtenances of academic freedoms, such as publication.

Kiley: Well, I believe that. I think that was one of Herb's great contributions to Genentech. I've mentioned before some of the other advantages we had at competing for those people: quick decision making because we weren't stratified or hierarchical, ability to offer equity participation, the fact that we weren't entirely grown up and so could tolerate, indeed encourage, a sometimes slapstick atmosphere.

But at the end of the day, as this science began to break, it was just terribly exciting, most of all to scientists. And the opportunity to practice it without indulging in grantsmanship had to be very alluring. Grants are administered by the grizzled warriors and veterans of earlier revolutions, and this was a young man's science or a young woman's science. Genentech gave them an opportunity to do what they wished without putting themselves through the filter of someone holding onto his academic tenure through politics and his ability to control grants, and so on.

Hughes: It was a youth culture, was it not?

Kiley: The best evidence I have for that is that the first time I went to a company picnic I was the only one there with children.

Hughes: [laughs] And you were not so old yourself.

Genentech and other early companies came under attack by some sectors of the academic community because of their practice of publicizing an achievement before it was published. I believe in the cases of somatostatin, growth hormone, and insulin, the press conferences came before scientific publication. The paper might have been in the press, but it hadn't come out. Spyros Andreopoulos in Stanford's public information office wrote an article, I think in 1985, in the *New England Journal of Medicine* which was entitled, "Cloning by Press Conference." It debunked defiance of the academic tradition in which you don't talk publicly about your work until it's published.

Kiley: Well, I think Mr. Spyros Andreopoulos might have been painting the lily a little bit there. As a general principle, Genentech strove to comply with the mores of the scientific establishment in its announcements. It is very common for things to be announced after a--

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Kiley: --manuscript has been accepted, sometimes earlier at a scientific meeting in the form of a talk. It is possible Genentech might have missed on one or two occasions where, for example, a press conference was being driven by another participant in the collaboration. That may have happened in the City of Hope case. I don't recall.

Concern about the Commercialization of Biology

Kiley: In the earliest days of the biotechnology industry, there was a great deal of academic hand-wringing about the commercialization of what hitherto had been a comfortably pure science. The subject was controversial and those people that were polemically opposed to commercialization often found it convenient to decry the possibility postdocs would be harnessed to the commercial ambitions of company founders resident in academia, or that publication would be deferred, or that materials would not be freely shared.

Now, to a certain extent, the diminution in the volume of shared materials has more to do with the growing perception that they are valuable than it has to do with commercialization of any kind. At a time when bits of DNA were laboratory curiosities, academicians were much freer in handing them about to their colleagues than they were once their ability to unlock molecular puzzles became more apparent. I think it would be interesting to graph the stringency of university materials transfer agreements in the last several decades against the growth of industrial sanctions against misuse of research materials. I expect you'd find those graphs nearly convergent.

Hughes: Yes, I agree with you.

Kiley: Look, it is the fact that a great deal of innovation in molecular biology has come from industry and has been published. Any fair look at the literature will suggest private investment has led to a great addition to the public fund of knowledge about molecular biology.

Hughes: And biotech companies and Genentech in specific played upon that. Witness the graphs of the increasing number of publications in Genentech annual reports, beginning in 1981.[1]

Kiley: Well, there is no rose without its thorns, and there are some thorny issues involved in that sort of publication growth. If an organization comes to the point where scientists are being rewarded in significant part by reference to their publication history, then the number of times any given scientist is a lead author or senior author on a paper becomes important. That tends to a proliferation of research projects, which in turn can be debilitating from the standpoint of focus. If an organization comes to a point, as Genentech did at one time in its history, when a predominant part of its research and development resources had to be focused on tPA, the flagship project, to the exclusion of funding on other individual projects that could lead to other publications, then morale is affected, retention is affected, and so on. But it's what happens, from a financial standpoint, when you have to push elephants through keyholes. So as in everything else in life, what's needed is balance where you're trying to do something that's

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[1]See, for example, Genentech annual report, 1981, p. 14.

very hard. And there has to be a certain amount of give and take and sacrifice and reciprocal reward.

The American Type Culture Collection of Microorganisms

Hughes: Is there anything that you care to say about the requirement to deposit a microorganism in the American Type Culture Collection?

Kiley: The practice is a hoary one in the patent business, and it began because the law requires that you enable the public to practice your invention by giving a sufficient explanation in the patent document how to do it. But when people began using mutated microbes for particular purposes, like the production of antibiotics, our descriptive powers were inadequate to the task of describing the microbe that, if you will, laid the golden eggs. So how to enable the public to practice that invention and make the golden eggs once the patent has expired, if you can't describe how to get the microorganism which may have arisen by random mutation in an irreproducible way?

Well, the answer sprung up: we will make a deposit [of the microorganism] in what is called the American Type Culture Collection, the way we would deposit a book in a library. And you'll be permitted to check the book out, simply by taking a copy of it away. And since the book on deposit makes more copies of itself, you don't have to return your copy. The only thing you have to undertake to do is make no commercial use of it until the patent expires.

Well, when we had a bug that made somatostatin, the question arose, must we deposit the somatostatin-making bug in order to fulfill our side of the patent bargain? And my view was perhaps we should not do that because in those days we were concerned that people might check the bug out of the library and take it overseas and use it. And it was unclear whether patents would issue on bugs overseas. It was even unclear whether patents would issue on bugs in the United States, at all times prior to *Chakrabarty*.

Meanwhile, we had used skills we thought were rare in industry and perhaps in the world at large to create not only the somatostatin gene, but the other cellular machinery that turned it off and on. We thought that if that went into someone else's hands, that would give them undeserved lead time. Lead time was an advantage to us. So my recollection is I chose not to deposit, with the idea that, unlike the case in earlier years when one could make new bugs only by random mutation, we could describe in print how to make this bug. But having done that, we would have fulfilled our obligation. Let someone else go take the time, tears, and sweat investment to make it happen.

I think at some later time, we did make the deposit. We made the deposit after the appellate courts had concluded you can make the deposit any time up until the issuance of the patent; and so we were able to hedge our bet by a later deposit. And perhaps by that time the skill in the art had increased to the point where the lead time our failure to deposit represented was no longer significant.

Hughes: I wonder if the Cohen-Boyer patent application had prompted the decision that the deposit could be made any time up to the issuance of the patent. One of the many issues that arose when the second and third Cohen-Boyer patents were pending was that no deposit of the microorganism had ever been made and consequently that fact should throw out the patent application. The objection obviously didn't hold water, because the patents issued.

Kiley: I don't recall.

Hughes: I gather from what you're saying that it was a given that *E. coli* that made somatostatin was a new organism?

Kiley: Well, considering that somatostatin is a human brain hormone, I would say that's a safe bet.

Hughes: Yes, but you could say, there must be existing deposits of *E. coli* in the culture collection, why do I have to give you this particular variant?

Kiley: Well, that's right. In fact, it was a strain one could get elsewhere, and then one had to construct the plasmid which incorporated the promoter region, the structural gene, the center of origin, all the other business that influenced efficiency in expression.

Hughes: Your argument was that the information was there in the patent. "If you guys want to make the organism, go ahead and do it, but we're not going to hand you the live entity by putting it in the culture collection."

Kiley: That's right. But it was a decision over which we wrung hands for a time before we made it. I think the logic was good.

Hughes: One after another, there must have been novel issues like this appearing, novel, not only in your experience, but in any intellectual property attorney's experience. The issues had to be solved, precedents had to be established, and sometimes even court decisions had to be made.

Kiley: Well, that is true in one sense and not in another. The genius of the patent system is that, viewed most usefully, there are very few rules. But the rules that are there are pole stars for decision: I must teach the public how to practice this invention, but no more. It must be new in every respect or rather in the sense that nothing precisely like it ever before existed. It should be useful. It should be unobvious. End of story.

Now, if you apply those precepts to complex factual situations in a consistent way, they tell you what the answer is. Obviously the devil's in the details, and people can fight for years in court about whether the precepts were properly applied in a particular concrete setting. But they are guides for decision. I think when we make the patent system more complicated than it needs to be, then we're led into conniptions and problems. [tape interruption]

Genentech Culture and Financing

Hughes: I wonder if the creativity that you have been describing for Genentech in terms of its scientific productivity was mirrored in other aspects of corporate function?

Kiley: I thought we were rather creative in our approach to structuring our corporate relationships, but more importantly in making Genentech a good place to work. And that was in part a function of Bob's great cheerleading ability, his management by walking around, the shared ownership all of us had in the company's successes, the financial sharing that went with that, Genentech's sometimes slapstick culture; [and] things like creating what was for its time the largest corporate daycare center in the West and perhaps in America, leading most recently for I think the third year in a row to Genentech's being high on the list of *Fortune* magazines 100 best companies in America to work for.

Certainly the company has been creative in financing itself. We went public at an unprecedentedly early stage for a company of our time. Fred Middleton, who was Bob Swanson's one-time fraternity brother and the company's first chief financial officer, now a successful venture capitalist, was very creative in financing endeavors. I think it's fair to say Fred created something now referred to as restricted stock, and later convertible restricted stock, so employees early on could buy cheap stock in the company at a significant discount relative to preferred stock and begin vesting that.

Fred's creativity was never better displayed than in the clinical R&D partnerships we used to finance in substantial part clinical trials for human growth hormone and gamma interferon and in particular tissue plasminogen activator or tPA. Those were created at a time when tax shelters were popular, and a substantial tax deduction was available for investments in research and development. We were able to make the case that clinical research was entitled to tax deduction, on the one hand, because there was a risk involved, and on the other, risk could readily be borne where the money was devoted to proving a substance of known function and ordinarily made in the body could be made by recombinant DNA and work in the clinic. So investors could buy shares in these partnerships and have immediate tax advantages with no more risk than asking whether growth hormone would make children grow or a clot dissolver would make clots dissolve, as demonstrated in the clinic. Later when the tax exemption went away, funding of this kind nevertheless remained popular because it could turn into a stock market play--the investors would have an option at the end of taking their return by way of royalty or through being bought out of their royalty with shares of the company.

Fred cooked that up all by himself and solved for us the dilemma that mere licensing revenue wasn't sufficient to fund clinical trials at a time when we had no product sales to speak of to do that. We couldn't license enough things out, without emptying the pantry, to pay for the clinical trials of the things we chose to keep for our own account, and Fred solved that one. I think he's entitled to a lot more credit than people outside the financial community have given him for making Genentech what it became.

R&D Clinical Partnerships

Hughes: Do you care to say anything more about the clinical partnerships? Was that also a Middleton creation?

Kiley: Well, the R&D clinical partnerships are what I've been referring to.

Hughes: There are many?

Kiley: Yes.

Hughes: I thought it was one entity under which all the clinical trials operated.

Kiley: I think there were at least three of them, perhaps four in all. At least the first two returned five times cash on cash to investors.

The Agreement with Kabi Vitrum on Human Growth Hormone

Hughes: Have we said enough about the initial human growth hormone agreement?

Kiley: The human growth hormone agreement with Kabi, which now involves, as its successor in interest, Pharmacia and Upjohn, is the subject of a rather substantial arbitration proceeding underway between Genentech and Pharmacia and Upjohn. I testified at length over a matter of three or four hours just recently in that. A decision is probably to be expected within the next month or so.

Hughes: What is the contention?

Kiley: One I find very curious. As the Kabi people now claim to read the agreement, at the end of the term, Genentech was to turn over to them not only title to the growth hormone-producing microbe that we provided to them in fulfillment of our part of the bargain, but also all the stocks we retained for our own purposes. In effect, to leave the business or make a different organism altogether, if we wish to remain in it, and go through the FDA cycle again at enormous expense. It is as if someone bought an automobile from the Chevy factory and, on the strength of his purchase agreement, claimed to be entitled to the whole inventory of automobiles in the factory.

Hughes: Tell me a bit more about the relationship with Kabi, including its scientists. I'd be interested in hearing about any technology transfer that must have occurred.

Kiley: I first entered into the Kabi discussions at a time when Bertil Åberg, head of research at Kabi and a great champion of the new biotechnology, flew to New York with Kabi's head, a fellow by the name of Bengt Andren, to talk to Swanson and me about structuring an arrangement under which Genentech would produce microbial human growth hormone for Kabi's purposes and our own.

Earlier, Swanson had approached Kabi, knowing it to be a leading supplier of human growth hormone extracted from cadaver pituitaries, and believing that recombinant DNA would provide a superior source for that material which was then in very limited supply. Åberg invited Swanson and Boyer to visit him in Stockholm. Swanson was at a stage when he couldn't afford the plane ticket, and so he bald-facedly asked Bertil to pay their plane fare, and he did so.

Åberg was a true visionary, a real renaissance man. He played the harpsichord for the Stockholm Symphony [and was] an accomplished scientist in his own right. He sat on various of the Nobel committees. He was involved with the Karolinska Institute. Before almost anyone else in the pharmaceutical industry, he grasped the great power of recombinant DNA to transform business and to his dying day took great pride in having entered into the first ever partnership agreement between a biotechnology company and a pharmaceutical company. I think he did that on or about the eleventh day of August, 1978, beating Eli Lilly, our insulin partner, by on the order of two or three weeks. And indeed, it was Bertil who later gave us encouragement when we approached Kabi, asking them to return to us their shared growth hormone rights in the United States when they were somewhat retrenching from their plans to expand into this country. A wonderful man.

Hughes: Did he truly succeed in making recombinant DNA an in-house technology for Kabi?

Kiley: Well, yes, he did. We, under his tutelage, transferred the technology to Kabi for the recombinant production of growth hormone from *E. coli*. I recall vaguely the parties had some disagreement over how best to purify the material and formulate it. Kabi justifiably felt it knew a great deal about handling growth hormone, albeit from a different source. How it got resolved, I don't honestly remember, although it is possible that in the end the companies registered in their respective territories two somewhat different manufacturing technologies for the same product.

Hughes: [tape interruption] Did these partnerships, these contracts with pharmaceutical companies, serve as a model for other young biotechs starting up in the 1980s? Or was everybody doing it in their own way?

Kiley: Oh, I'm sure techniques varied from company to company. Necessity is the mother of invention. One had to proceed by way of partnership if you were starting from square one with meager financial resources. The particular ways in which the partnerships were structured undoubtedly varied greatly. I think Genentech can take some credit for establishing what became at least the classic uber-structure of these arrangements, and that is, some money up front, support for ongoing research and development, the postponement of significant lump sum payments until risk is reduced by the achievement of agreed milestones, and ultimately participation, either through profit-sharing or royalty on net sales, in the commercial rewards.

Extraterritorial Licensing Rights

Kiley: We also find commonly in agreements of this kind, perhaps originating with Genentech, the notion of peeling off extraterritorial rights--that is rights outside the United States--to potential

partners as a means of gaining some revenue, while holding the home markets in the hope that you can make yourself into a real company by exploiting them. American companies are very favored relative to companies abroad because the American domestic market for pharmaceuticals is the greatest in the world and there is enough here upon which to grow a company.

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Kiley: In many countries the domestic market is not enough to sustain a company, and so right from the get-go you have to build sales and marketing beyond your borders and in unfamiliar law systems. American start-ups have a great advantage because of the disparate share of world markets we represent.

Genentech-UC Legal Relationships

Hughes: Well, we've talked about Genentech's relationships with pharmaceutical companies; what about universities, and in specific the University of California? Is there anything particular to say about what it was like to negotiate with university administrators?

Kiley: Well, there are two large questions hidden in that one. I've never dealt with anyone in the administrative offices of the University of California who has treated me or my colleagues other than in a civil and professional manner. That is not to say we haven't had disagreements and serious ones.

When biotechnology began, the patent and licensing operations of the University of California were somewhat unsophisticated. It largely was not the fashion for academicians to go to the university administration to obtain patents on subjects of their researches. I'll never forget Roger Ditzel, who came to represent the University of California Systemwide in patent licensing, tell me that until the Boyer-Cohen patent, the largest single source of licensing revenue for the University of California was on plant patents for strawberries. Indeed, before Ditzel's time, patents arising from the University of California at San Francisco were administered through an office of contracts and grants by a woman, not a lawyer, by the name of Josephine Opalka. I think that suggests in the mid-seventies the focus within universities was much more on government grants and much less on patents than is the case today. More recently, federal support for research at the university level has gone somewhat on the wane relative to the importance of industry's ability to take things right from the university laboratory bench and move them into the clinic with relative alacrity. So all of the universities have got much more sophisticated and aggressive in identifying intellectual property within the university and in dealing with it outside.

Now, having said all those nice things about university administrators and the history of their evolution in the intellectual property field, I have to say Genentech's relationship with the University of California has had elements of love and hate.

The University of California was very unhappy with me because I could not [in their eyes] justify adding a University of California inventor to the first patents Genentech filed.

Subsequently, the Regents of the University of California came after Genentech and Roche, having learned that the messenger RNA that was used in cloning alpha interferon was extracted from a cell line that turned out to have originated at the University of California at Los Angeles. Later a controversy arose over Genentech's hiring of two people from the University of California at San Francisco's Goodman and Baxter laboratories, leading to a settlement of non-patent aspects just prior to our public offering and only within the last year or so to a substantial settlement, putting to an end the patent aspects of related controversies.

Now, at the same time, Genentech has been often a collaborator with workers at these several universities, has been good to their out-placement people in terms of providing jobs to the fine researchers that emerge from that system, has conducted clinical trials within various arms of the University of California, and so on. I think it's fair to say whatever the sometimes contretemps between the two institutions, both have benefited from living in the same neighborhood.

Observations on the Biotechnology Industry and Factors Affecting It

Biotechnology Clusters in the U. S.

Kiley: It's no accident the Bay Area has become a center for biotechnology in the nation. Companies grow up in areas whose intellectual waters emerge from academic highlands. UC Berkeley, UC San Francisco, Stanford, amongst them, are the pillars of the biotech community here.

Hughes: What you say is certainly true. But one could say, there are plenty of premier research universities in this country; what's so special, other than the three universities you mentioned, about the Bay Area?

Kiley: [pause] Biotechnology centers of excellence, if you look around the country, seem to be located near academic institutions that get a substantial share of the federal research dollar, principally from the National Institutes of Health. So we find them in San Diego around UC San Diego, Scripps [Research Institute], and so on; here, around the universities I've mentioned; in the Northwest, around the University of Washington; in Boston, M.I.T., Harvard in particular, Mass General; nowadays in the Bethesda area, around the National Institutes of Health; and the Research Triangle [Park] of North Carolina because of Duke University, in particular. So in a sense, they are sproutlings that grow up from the root system of the medical research establishment in the United States.

Having said that, it's undeniable that from a cultural standpoint, some regions of the country are more forward-looking and risk-accepting than others. And that's certainly true of California with its origins in the Gold Rush, with the more recent example of Silicon Valley that grew up around electronics and then the computer, and now all of the infrastructure that follows in the wake of that--from an accountancy, venture capital, law, and kindred standpoint--to support new risk enterprise. I think it's a combination of a climate fertile for entrepreneurialism and deep federal investment in medical research that supports fine institutions of learning, that train good people who are reluctant to leave the salubrious

California climate if a way can be found to afford them housing here. Thus the biotech industry in the Bay Area.

The Bayh-Dole Act, 1980

Hughes: Let's talk about the Bayh-Dole Act, which was passed in December 1980. As you know, the intent was to take commercial advantage of the research discoveries at American universities which had not been fully utilized in a practical sense, as shown by the poor rate of patenting and licensing.

Kiley: I think it's true not only of university researches but also researches within the various federal laboratories. For the longest time, the notion had been taxpayer-supported research ought to lead to cheap goods or free goods and that there's something wrong with a patent issuing with licenses to only a single entity [which] can then control the resulting goods and charge monopoly prices for them. From an emotional standpoint, it's easy to understand why people would feel that way. But from an intellectual standpoint, it leads to patents to no purpose. That is, the innovation they represent lies unused because without some measure of exclusivity, no one will make the deep investment required to turn them from paper into something of tangible benefit to the public. That's nowhere more true than in the pharmaceutical industry because of the huge costs of satisfying the Food and Drug Administration before a product can be sold. No one in the pharmaceutical industry will bear those costs unless he can recoup them and more by controlling price, by controlling product over the term of the patent.

What the federal government, proceeding under the old and what I call emotional philosophy, the politically expedient policy, did was forbid universities to grant exclusive licenses to patents arising from federally funded research. In effect, that was any patent touched in any way by federal funding. If the federal government kissed your innovation, it was pregnant with this injunction against exclusive licensing. Universities could, under some administratively worked-out exceptions, license exclusively after an arduous journey that attempted nonexclusive licensing. But who was up to that task?

So the Bayh-Dole Act, recognizing all of this, for the first time permitted exclusive grants, subject to a government march-in where public health and welfare demanded. That led as much as the biotechnology revolution to the reinvigoration of university intellectual property licensing operations. We're getting much more benefit from the federal research dollar and from university research as a result. It's undeniable.

Hughes: So Bayh-Dole in your view had a big impact.

Kiley: I never sought to quantify it, but I think it's plainly had a terrific impact in growing the biotechnology industry, in legitimizing industrial research in molecular biology in the eyes of academicians, who, having been given some incentive to learn more about the commercial world, now find it less forbidding and more useful to them. To paraphrase Lincoln, at an academic level the Bayh-Dole Act "lent the fuel of interest to the fire of genius."

Testifying at a Congressional Subcommittee, 1983

Hughes: In August of 1983, you testified before a subcommittee of the U.S. House of Representatives, called the Subcommittee on Banking, Finance, and Urban Affairs. How did that come to be?

Kiley: This was a circuit-riding subcommittee going around the country looking into what it called "sunrise and sunset industries," sunrise industries being those building up around new technologies; sunset industries being the sorts of heavy industries that seemed to be moving overseas--steel, shipbuilding, to some extent automobile production, and so on. Particularly coming out of the years of "economic malaise," to which President Carter had referred, the question was how can we encourage the sunrise industries and what can we do about the sunset industries?

My focus obviously was on the former. My point in the testimony was to describe why the sun was rising on certain kinds of industries in the United States, what it was about America that fostered the growth of technology industries, and what characteristics of Genentech I thought were important to its success--for example, that we were collaborative, that we celebrated what I called "firstness," that we were risk takers, experimentalists, and problem solvers. The point was to tell them what it is about this country that fosters the growth of sunrise industries. Then I had a rather specific shopping list of things we thought Congress ought to do to promote the growth of new industries.

Looking at it now for the first time in seventeen years, I must say that it's rather prescient. We told Congress we thought patent-term restoration should be encouraged, and that was later enacted. We told them we thought the export laws needed to be changed, permitting drugs not approved in the United States to be sent overseas in appropriate circumstances. That later was enacted. We asked for extension of the research tax credit and for streamlined regulation, in particular within the FDA. Both of those requests ultimately were enacted. And I believe we also asked that Congress consider cutting the capital gains tax rate, which it subsequently did.. All in all, I must say Congress exceeded my expectations in the fullness of time and confess those expectations were not large at the time.

Court of Appeals for the Federal Circuit

Hughes: In October 1982, the Court of Appeals for the Federal Circuit was created.[1] What difference if any did this make to what you and your peers were doing, particularly as applied to biotechnology?

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[1]Reid G. Adler, "Biotechnology as an Intellectual Property," *Science* 224 (1984): 357-63.

Kiley: I don't know that we perceived any difference at the time. In the fullness of time, it's my opinion the creation of that court was a very big mistake. American jurisprudence is enriched by difference of opinion, and the dialogue and debate that goes on amongst different judges in different circuits living within different cultural eco-niches is important. Where real disagreement arises amongst such judges, the law works it out at the United States Supreme Court. What we've created in the case of the Court of Appeals for the Federal Circuit is a single patent court whose jurisprudence threatens in particular cases to become constipated by the lack of rich dialogue. In my opinion, it has proven to be unduly pro-patent, with the result that in some respects it's fair to say America is choking on patents and innovation is being stifled by them.

It is not a court that over time has had a history of bringing in new judges with demonstrable patent expertise. Its jurisdiction is broader than patents alone. Perhaps that's one justification. And the pendulum of its jurisprudence, after a decade at least of excess, may now be swinging in a useful direction. But for too long it's permitted patents of too great breadth to be upheld despite a relative paucity of underlying science or disclosure.

But the republic endures and I'm sure many can be found to say, against everything I've said, our economy is booming, at least until very recent days, booming in substantial part because of technology-based industries. So to the extent they've been permitted to grow up to our benefit, it's hard to knock the patent system. But think what better shape we might be in if we had a better patent system.

More on the Commercialization of Biology

Hughes: What do you think about the increasing commercialization and privatization of academic biology or discoveries therein? And should there be any changes made?

Kiley: If by your question you ask if I approve university researches leading to products that are good for people and good for the economy, the answer is of course I do. And it's hard to see how any academic researcher could feel otherwise.

But there is a more difficult issue underlying all that: whether universities will or companies will or individual professors will put so much emphasis on applied research that can lead to a commercial opportunity, that fundamental research suffers. And it is right that an awful lot of our economic strength has proceeded in unforeseen ways from the most arcane fields of research.

Herb Boyer once told me that gene-splicing--at least in the case of his own contribution--came from his interest in a field so baroque that it wasn't being pursued in more than a half dozen laboratories around the world. Well, from that and a significant contribution on Stan Cohen's part, we got recombinant DNA.

Suppose Boyer had been under great pressure to apply his energy and the funds available to him to making another antibiotic at a time when we were drowning in antibiotics. Well, we all would have suffered. And so what's needed is continued federal support, and to the extent

corporations can afford it, some encouragement on their part of the best science for science's sake. Let a thousand flowers bloom, there's sure to be a blue rose in there somewhere. And in many respects recombinant DNA was the blue rose that grew up in a garden not unduly tended and pruned. That's what science needs to continue to do for us.

I'm reminded of something I read in the paper the other day about Chief Justice Rehnquist calling on Congress to raise the salaries of sitting judges in the federal courts. He points out a Supreme Court clerk fresh out of law school may after a year or two of clerkship join a law firm and earn more than a Supreme Court judge. The gap between--

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Kiley: --federal judicial salaries and salaries of outside lawyers is leading talent out of the judiciary to our great detriment. If people are led out of the academic pursuit of science by greatly disparate salaries in the private sector, then education will suffer, science will suffer, and ultimately the economy will suffer. So ways have got to be found to make that right.

If the next question is how do we make that right without paying professors of poetry as much as we pay professors of electrical engineering or solid state physics or molecular biology, then the answer will have to be sought here at Berkeley because I don't know how to fix it.

Comments on the U. S. Patent System

Hughes: [laughs] Please comment on the strengths and weaknesses of the U.S. patent system.

Kiley: Sally, I've done that to a great extent, at least in discussing perceived weaknesses. The logic of the patent system is very compelling--that people pursue their self interest, and the best systems are systems that harness that interest to the public good. That's what the patent system does in so many ways--by encouraging the publication of information as against trade secrecy; by offering a stimulus to investment; in taking ideas from the point of realization through to application to the public benefit; and by giving every bright person a chance at economic success without regard to his or her origins. Witness all the wonderful stories about the Alexander Graham Bells and Eli Whitneys and Cyrus McCormicks of our world. Well, every generation has an opportunity to replicate those achievements because the patent system encourages them to do that.

Now, like any other system, its genius often can be found in its underlying principles and problems in its administration. The patent system is a government agency. It may be an agency that's not up to its task, particularly in areas where innovation comes fast and furious. It would be enhanced if it were permitted to spend its revenues on internal improvements rather than acting as a piggy-bank for Congress. Just as user fees permitted FDA to begin to fulfill its promise of streamlined operation, so the fees the Patent Office charges, which have gone up very substantially since I began practice, ought to be left to the Patent Office to improve its functions.

Hughes: What about your view as to the "first to invent" system?

Kiley: I don't have strong feelings to the point where I know what is right. My visceral reaction has always been patents ought to be given only to people who make inventions, and then to the first inventor. It goes against my grain to applaud the fellow who loses the race to innovate but wins the race to the Patent Office.

That's a peculiarly American and peculiarly egalitarian view of it. The first-to-file system one finds outside the United States is largely an excrescence of a European or Continental tendency toward ordered systems as against the messy democracy of the New World, and it has overtones of Napoleonic law. But having said all that, who knows what is best? In the end patent harmonization is probably good because the alternative is nations designing their patent systems to favor local industries and their own citizens.

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VI CORPORATE VENTURES BEYOND GENENTECH

[Interview 5: March 12, 2001] ##

Genencor

Hughes: Mr. Kiley, picking up the Genentech thread once more, you were director of a company called Genencor which was a Corning Glass venture in industrial enzymology. Could you tell me about that and when the company was formed?

Kiley: Genencor was formed relatively early in Genentech's history at a time when Genentech was still spreading itself across industrial applications and animal health care applications of recombinant DNA as well as pharmaceutical applications. A time came when we decided to spin out industrial applications. They went into a number of joint ventures of which Genencor was most notable. Corning Glass had developed some technology in which cells were grown on or proteins adhered to glass beads and had for a time decided to move aggressively into biotechnology. It proposed to do so with Genentech.

I remember a lovely dinner we had in the immediate advent of Genencor's formation. We had persuaded everyone at Corning to do it, other than Amo Houghton who ran Corning. We had Mr. Houghton out to a dinner at a private room atop the Bank of America building here in San Francisco, and to that dinner we brought David Packard who had just joined Genentech's board of directors. Amo Houghton thought of David Packard as the greatest living American, and before the dinner most of the conversation between Houghton and Packard had to do with Packard's stint as Assistant Secretary of Defense. Houghton looked on star-struck while David talked about battleships as if they were his bathtub toys. Well, we got through most of the dinner without a word having been spoken by David on the subject of the joint venture. Finally Houghton turned to him and asked him what he thought about all this genetic engineering, as it was then called; what he thought of Genentech. And then the roller coaster ride began.

Mr. Packard said he thought that Genentech was a promising company even though he hadn't invested any of his money in it. He thought that the technology was fascinating though he didn't understand it very well. And so it went, up and down. He was glad to be of service to the company but had joined recently and knew little of its immediate plans. Then with a twinkle in his eye, he said, "But you know, Amo, as I sit here and look around the table at these young fellers, why, they kind of remind me of myself when I was starting out." And that was it. That's all it took to persuade Mr. Houghton, and Genencor was formed.

Today it is a very substantial company with a multibillion dollar market capitalization, making thousands of products that range from the detergent industry to corn syrup production, starch conversion, and so on. Neither Genentech nor Corning any longer owns an interest in it. Each sold its interest over time to other companies. Finally, last year Genencor went public and now trades on the Nasdaq exchange.

Hughes: What goes into the decision to spin off an aspect of the technology and to form a new company?

Kiley: Many different considerations depending on the particular subject. So for example, in the Corning case, there was some complementary technology at Corning. Corning had a reputation as a brilliant company with whom to joint venture. They were participants in many successful joint ventures. The company had a certain luster which would illuminate Genentech by association. One spins things off when more resource is needed than your own company can muster. In the Genencor case, for example, the parties funded equally the activities of the company, but Corning primed the pump by making a $20 million equity investment in Genentech. Overarching all this is the need for focus if you're going to accomplish the difficult task of building a pharmaceutical company, which takes a lot of time and a lot of money. So at the outset you have a very broad platform of technology, sort of like a kid in a candy store. The scientists pick up things and run with them. Some value is created. You can't do everything yourself, but you try to extract some value by putting those projects where they can be advanced.

I know George Rathmann is fond of saying Amgen was very scattered at the outset, and so it was, on subjects ranging from chicken growth hormone to consensus interferons to diagnostics. But it's fair to say Genentech was somewhat diffuse in its earliest days as well, and it's easy to understand why that would happen. The technology operates at such a fundamental level it can be used to affect many aspects of life. Witness the creation of thousands of biotechnology companies in the ensuing years, all pursuing somewhat different objects.

Leaving Genentech, 1988

Hughes: You decided to leave Genentech in 1988, right?

Kiley: February 1, 1988 was my last day as an officer at Genentech--eight years to the day after I joined the company, although I continued to consult for the company formally for a number of years after that and informally since.

Hughes: Do you care to say why you decided to leave?

Kiley: Oh, I think that there were a whole complex of reasons. At the outset people in development stage companies get to wear lots of hats. Life is very interesting. Over time, as management fills out, the number of hats you wear shrinks, and I found myself of necessity in the latter years at Genentech spending more and more of my time in patent law, and particularly in respect of various litigations. Well, that was at the expense of continued active participation in corporate partnering and negotiations and so on, but more, it was something that I had done before. I was

reverting to lawyer type and I was more interested in continuing to move out into the business world. At the same time, recovering trial lawyers aren't very good delegators. They prefer to be hands on. And here was a company that had grown to several thousand employees. I found myself spending a lot of time sitting in meetings rather than doing things, and I found that somewhat discomfiting. I also had a disagreement with Bob Swanson, which I think told me the time had come to resign.

Having given my notice, I did remain in the company for an additional six months to ensure that the tPA patent would be obtained in the United States despite the pratfall in the British Courts. That was done. Then I left with the idea to take a year off and decide what I wanted to do next. Well, that year has become thirteen years, and during the first year, various things began to stick to me. I have been able to reprise the Genentech experience in some respects by getting involved as a founder or director of a host of biotechnology and medical device and related companies over time, and to this day I continue to enjoy looking over the shoulders of energetic young entrepreneurs and helping them, if I can, to pull off their visions.

Hughes: Tom, please describe the decision process which presumably steered you towards business involvement rather than to other forms of the law. Why business?

Kiley: Business is more multidimensional than law. I've referred earlier to the difference between a musical soloist and an orchestra member. I think trial law can be a zero-sum game. In that respect, it's less satisfying than playing in an arena where both sides can win, which is what results from good business combinations. And then simply the novelty of it. When you become capable of something, there's a natural tendency to go do something you're not capable of so you can learn new tricks.

Hughes: And what are those?

Kiley: One certainly is to supplant a lawyer's aggressive approach with an negotiator's more conciliatory approach; learn how to put yourself in the shoes of the people on the other side of the table and see the world from their perspective--identify their needs and try to satisfy those in a way consistent with achieving your own goals. And I must say it's all a little more orderly than trial practice, where you spend an inordinate amount of time jumping through hoops for fellows in black dresses who are upset at you because they work harder than you do and you earn more money than they do.

Evolving Corporate Culture in Biotechnology

Hughes: The success of a biotechnology company means, putting it simplistically, an about face in certain aspects of corporate culture. A spirit of innovation and being at the cutting edge and employees having a diversity of roles are not usual features of a larger company.

Kiley: I think that is right. People fall into two broad categories: what I would call company starters and company inheritors or maintainers. There are some people who like the action. They like doing something different every day. Other people derive satisfaction from doing the same thing the same way every day. Witness the distinction between a research scientist and a

manufacturing engineer. The research scientist by definition is looking for the new thing. It's what he does; it's what she does. A manufacturer on the other hand wants a reproducible process that gives the same product every time the assembly line is turned on. So it is certainly true Genentech became somewhat less interesting to some kinds of people as the company matured, and those people went off to start scores of other companies.

At the same time, the scientific excitement at Genentech has never abated, and so it's been successful in retaining a substantial number of the early scientists, even though many others have gone into new companies. If anything, I suppose the science at Genentech is more interesting today and more multifarious than it has been at any time in the company's history. In part that's attributable to the company's good work. In part that's attributable to the new dimensions biotechnology has turned up as it's been elaborated over time. It's now a very powerful science.

Athena Neurosciences

Hughes: Shall we turn to your post-Genentech story?

Kiley: I mentioned my involvement in other start-ups. I think the first of those after leaving Genentech was Athena Neurosciences, now a subsidiary of Elan Pharmaceuticals of Ireland. Athena was a venture-capital-backed company, whose founding vision was to pursue a cure for Alzheimer's disease by investigating the mechanisms of amyloid plaque formation in the brain. In its independent life, it failed utterly of that purpose. But under the stewardship of John Groom, a seasoned pharmaceutical executive, it built a tidy business in neuropharmaceuticals largely by in-licensing from major pharmaceutical companies who were focused on hitting home runs, the doubles and singles that they were willing to discard for want of large market size. Those in-licensed products were nevertheless large enough to make a difference to a small company.

In time, Athena was sold to Elan. Of course we were immediately sued by the class action lawyers who claimed we hadn't got enough for this company that had seemingly failed of its vision. But 99 percent of the shareholders approved the $635 million price we got for the company, which as Elan's fortunes rose, promptly went to a billion dollars. And I'm happy to say the class-action lawyers went away with empty hands. In more recent times Athena is back in the news because its Alzheimer's work seems to have yielded a promising vaccine against the disease. That vaccine is now in phase II clinical testing and is beginning to generate some substantial excitement. So maybe it is right that all comes to he that waits.

CellPro

Technology Platform

Kiley: During Athena, I came to CellPro as it was being formed. At the request of Brook Byers from Kleiner Perkins, who asked me to accompany Joe Lacob to Seattle and help license into the company a technology from the Fred Hutchinson Cancer Research Center there. The technology had been invented by a founder of the company, Ron Berenson. It permitted collection in a continuous manner from patient blood of stem cells that give rise to all cells of the blood system, including the immune system cells. These are cells that are often killed as a side effect of aggressive chemotherapy and radiation when cancer is treated. The notion was to rescue the stem cells from the patient before treatment, store them, and then return them to the patient after treatment to reconstitute his blood system. CellPro technology permitted the extraction and return of a tiny pellet of cells that made unnecessary the extraction from and return to a patient of liters of bone marrow.

Don Thomas of the Fred Hutchinson [Cancer Research] Center had received the Nobel Prize for pioneering bone-marrow transplant and was an early advisor and mentor to CellPro founders. I became a director of CellPro and served there for five or six years. The company's technology ultimately found its way into upwards of sixty clinical trials throughout the world. It was run by Richard Murdock, a bright young man we hired from the Fenwall Division of Baxter Healthcare. Baxter would become a big part of the CellPro story and of the company's ultimate demise.

CellPro-Baxter Litigation

Hughes: What was that about?

Kiley: Shortly after CellPro was formed, we identified the first of what became a series of patents issued in the name of Curt Civin at Johns Hopkins University. The patent purported to claim an antibody that bound to a stem cell. We had doubts about the validity of that patent but were happy when we learned licenses would be made available under it to all comers. The patent had been licensed by Johns Hopkins to Becton-Dickinson. In turn, Becton-Dickinson licensed to Baxter Healthcare the therapeutic applications. We looked at the terms proposed by Baxter and made a counter proposal.

Two or three months passed without word from Baxter, and then we were told that for CellPro, Baxter had a special plan. Rather than simply license the patent in exchange for royalty as had been proposed earlier, Baxter would require of CellPro exclusive access to its product for overseas markets and nonexclusive access in the United States. That would have left the company mortally wounded: no technology to trade off in markets we couldn't access; more importantly, the prospect of competing with a huge corporation in domestic markets, with no technology edge.

The company responded by bringing suit in the district court in Seattle, seeking a declaration that the patents were not valid and that the patents were not infringed by CellPro's device. Fortunately by this time CellPro had become a public company and could muster means for what became a Herculean struggle. Because of the web of ownership and license rights, we sued all of Becton-Dickinson and Baxter and Johns Hopkins University. Before long, the court in Seattle dismissed the case. Baxter had asked that it be dismissed because it claimed there was no justiciable controversy between the companies, and so its patent rights should not be put under judicial scrutiny. The court dismissed for another reason after finding there was a controversy. It dismissed because it said Johns Hopkins was a necessary party and could be not found in the State of Washington for jurisdictional purposes.

Baxter, who had disclaimed any justiciable controversy between the companies, promptly sued CellPro in the Delaware district court for patent infringement and issue was joined. The case was tried to a jury. Judge Roderick McKelvie presided. I must say the executives of CellPro found the whole matter agonizing. That can be true of trials, because years of work are suddenly at risk of the judgmnt of jurors untutored either in law or technology. Particularly where your only business is at risk of an adverse outcome, you see a lot of your life passing before your eyes while the jury is out. Well, the jury came in and found that of the four patents, none were valid, none were infringed. And a newsletter called *Biocentury* hailed in its headline "CellPro's Complete Victory."

Two Catastrophes

Kiley: Sometime after that I left the board of directors of CellPro to engage in other activities. After my departure I learned two terrible things. The first was that Judge McKelvie had thrown out the jury's verdict, allegedly for the reason that he had misinstructed them in the law, and he had set the matter for retrial. The other terrible thing I learned was that Rick Murdock, CellPro's CEO, had been diagnosed with mantle cell lymphoma, a stone-cold killer of a disease. And so in the run-up to the new trial, Rick had another battle to fight, and that was to live despite grim survival statistics common to this disease. He would have to have aggressive radiation and chemotherapy. He would need the CellPro device to save his life.

But there was a problem with the CellPro device when it was used for cancers of the blood system, and that is when you take out the stem cells, the sample may be contaminated with cancer cells. In that case, when you reinfuse the stem cells, you reimplant the cancer. The answer would be to make a second generation CellPro device that collected stem cells but purged the cancer cells by getting them to stick to an antibody specific to them in a way that permitted separation from the stem cells.

Employees of the company went into overdrive to make the second generation device, and in the course of eight weeks, just in time, succeeded in building a device that the FDA would permit be used to treat Mr. Murdock. He was treated, and the device saved his life. He's written a fascinating book called *Patient Number One*, in which he describes not only his battle against cancer and the company's heroic efforts to save his life, but also the patent battle that was going on at the same time.

So in time the company went back to Delaware. But by the time of the new trial, the judge in a series of legal opinions and decisions had eliminated every defense of the company against the patents.

Hughes: Why that about face?

Kiley: I can't read the judge's mind; I can read only what he says. I think his legal opinions are ham-handed. It became clear over time that he was very angry at CellPro for reasons unclear to me. It's very unusual for complex questions to be so completely decided as matters of law, and particularly ironic they could be decided in the wake of a trial where issues of fact were decided the other way by a jury. Nevertheless, CellPro was left with no defense. And the second trial turned out to be about nothing other than two questions: one, what were the extent of the patent holder's damages; two, would the company be found to be a willful infringer such that damages would be increased at the judge's discretion?

Of course the new jury was not permitted to know we had won the first case. Indeed the judge instructed the new jury that, in effect, he had already determined that no rational person could have concluded either that the patents were invalid or that the patents were not infringed. And now it was up to the jury to decide whether we were unreasonable in having concluded the contrary. Faced with that instruction, it is not surprising the jury found CellPro to be a willful infringer. Our jury consultants interviewed the jurors afterwards and learned they had figured out there had been an early trial, and they inferred that we had lost, otherwise why would we be back in court? They were quite surprised to find they had determined us to be willful infringers while a jury of their neighbors had earlier concluded we were right about the patents. With the jury's verdict in hand Judge McKelvie trebled damages and entered an injunction that would permit CellPro to continue to make its devices available only until Baxter could complete development of what it claimed to be a comparable device.

After that, CellPro would be obliged to withdraw from the market, and in the meantime, it would be required to pay Baxter so great a percentage of the sales price of its devices that every sale would constitute negative earnings for the company. The company was nevertheless obliged to operate under those terms during the pendency of its appeal if it was going to continue to support clinical trials that were going on around the world.

Hughes: Was it the judge's intent to stop those clinical trials?

Kiley: It is common following verdicts of patent infringement to enjoin the infringement unless that is contrary to public health and welfare. The court concluded we could continue the activities for the benefit of patients, but only until the Baxter alternative became available. CellPro's hope was that the judge's various decisions would be reversed on appeal, and it would then reap the fruits of having continued the clinical trials. In the event, the court of appeals upheld the jury's verdict and found not enough error in the district judge's opinion to make a difference to CellPro.

The Bayh-Dole Act and an Aborted March-in

Kiley: CellPro had in the meantime engaged Lloyd Cutler, former counsel of the President of the United States, to submit a petition to the National Institutes of Health. The several patents involved in this manner were the result of government-funded work. Under the Bayh-Dole Act, where government has funded patented work for the benefit of public health and welfare, it may march in and demand that the patent holder or license holder under it grant licenses to others on reasonable terms. We believed no better case ever existed for NIH to march in, given the clinical stakes.

Hughes: How common was it for NIH to march in?

Kiley: NIH had never done so. That feature of the Bayh-Dole Act has never been implemented. We thought we had a compelling case. But following the petition, university offices of technology licensing all over the country rose in revolt, claiming that if the government ever marched in, a pall would be cast over university efforts to license exclusively inventions made in those institutions. Finally, [NIH Director] Harold Varmus issued a lengthy decision denying the petition. He did so largely on the basis of assurances by Baxter that the Baxter system would shortly become available and satisfy patient needs. So with its loss in the court of appeals and the unwillingness of NIH to march in, CellPro was left with an empty sack, whereupon the class-action lawyers came to take away the sack.

In the final analysis, the company was sold to a company called VimRx which was a stalking horse for Baxter Healthcare itself. I'm happy to report that Mr. Murdock is alive and well, so it was all worthwhile, and when I last heard he was in the San Francisco Bay Area as the CEO of a company called Kyphon, which has an ingenious suite of new instruments and devices for the treatment of the spine.

Hughes: What was the source of the stem cells? Blood?

Kiley: Stem cells are the source of human beings.

Hughes: Yes--

Kiley: I've mentioned earlier the embryonic stem cell. The cells CellPro collected were not embryonic stem cells but rather cells that were pluripotent in the sense they give rise to the blood system, but to nothing else. So they stand further up the differentiation tree than the sorts of cells Geron is working with.

Hughes: Were there political ramifications, as there are now concerning embryonic stem cells and fetal cells.

Kiley: There certainly are political issues affecting embryonic stem cells. The CellPro cells were quite another matter. Before CellPro, bone marrow transplant involved scores of aspirations of marrow from pelvic bone, leaving patients feeling as if they'd been beaten with a baseball bat. After CellPro, a patient would sit down with a plasmapheresis machine, blood would run out of his arm through the device and back into his arm, and in that relatively painless way the lifesaving cells could be rescued and stored for reinfusion. No embryos in it.

[tape interruption]

Hughes: Tom, that doesn't sound as though it was a very happy experience. Were there other litigations that were similarly dramatic?

Kiley: I find something dramatic about all litigations. [laughter] Intellectual property is at the heart of the biotechnology industry. Intellectual property can be contentious. Other companies that I've been involved in have been obliged from time to time to defend themselves.

GenPharm and Cell Genesys

Kiley: Indeed, as I was sitting in Delaware preparing my testimony in the second CellPro trial, I was also on the telephone settling litigation between GenPharm and Cell Genesys having to do with mice that produced human monoclonal antibodies. Ironically, those two companies were run by Genentech alumni. Steve Sherwin was CEO of Cell Genesys; Jonathan MacQuitty CEO of GenPharm

GenPharm was a very interesting company, another that I became involved in at the request of Kleiner Perkins. It started as two companies. One wanted to make transgenic mice, and indeed it was incubated before its funding at Genencor where McQuitty was then employed. Another Genentech alumnus, Herman de Boer had in the meantime gone to Holland and formed a company to make transgenic cattle. These two groups got put together and under the name GenPharm were funded by venture capital.

The first success came in bovine genetics when the workers under de Boer, operating in Holland, succeeded in slipping a human gene into a calf that became "Herman the Bull." Herman was the progenitor of a line of cattle that could now express this human gene. The human gene encoded an anti-infective agent ordinarily found in mother's milk, but never in a cow. The notion was producing it in a cow would lead to better infant formula. As you might imagine, this gene-spliced cow was a matter of some controversy in Europe. It did not go unnoticed by the Green Party, which--

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Kiley: --expressed its distaste for the work. We were obliged to get the approval of both houses of the Dutch parliament. We were mentioned favorably in the Queen's birthday message as doing work important to the dairy industry, an important part of Holland's economy. The transgenic cattle business that started in that way now exists as a spinout company in Europe trading on Easdaq and called Pharming, B.V. It's working very closely with the American Red Cross to produce various blood proteins in milk rather than by extraction from human blood with the attendant risk of infection.

Pharming was spun out of GenPharm in part because a time came when GenPharm couldn't raise finance, and it was thought the transgenic cattle business could be separately financed as a European company. That proved to be true. GenPharm was unable to raise finance because it had been sued by Cell Genesys who alleged its trade secrets had been misappropriated as they

bore on the production of human monoclonal antibodies and transgenic mice. It was known the two companies were competing in efforts to make a mouse that could be immunized so as to produce hybridomas that would express human monoclonal antibodies. Both companies ultimately succeeded in making such mice, but Cell Genesys had succeeded in going public. GenPharm was in registration for its public offering when the trade secret suit--which I regarded as completely bogus--was filed, and our financing window promptly slammed shut because of the litigation overhang.

I'm under some constraint in what more I can say about the lawsuit because of the way in which it was settled. But it is a matter of public record that after aggressive discovery, we were able to better understand what inspired the suit and the paucity of its allegations. We filed a very lengthy antitrust complaint against Cell Genesys. Coincidentally that came at a time when they were on the cusp of a merger. They found the overhang of the antitrust complaint rather awkward, and so the matter settled.

My old friend Jim Gower, formerly vice president of sales and marketing at Genentech, was a member of the Cell Genesys board. He was delegated by his people, as I was by mine, to get together and see if we couldn't make peace, and we did so. The case settled on the basis that a very large sum of money was paid to GenPharm by Cell Genesys, and the two parties cross-licensed their mouse technology.

The next thing that happened was Cell Genesys spun out a company called Abgenix to pursue the mouse opportunity and GenPharm, exhausted by the long battle, sold itself to Medarex. Today those two companies are world-renowned in human antibody production. Each of them has at times sustained multibillion-dollar market valuations, and I think it's fair to say that Cell Genesys and GenPharm both have something to be proud of.

Political and Ethical Issues

Hughes: How did GenPharm and the other companies handle the political problem of the Green Party opposition to transgenics?

Kiley: Happily from my standpoint, most of the sound and fury seems to have been focused on agricultural applications and particularly plant applications of genetics. The Harvard xenomouse and the GenPharm HuMab mouse seem to have drawn far less fire. In part, these controversies are a function of risk-benefit politics, if you will. It's easier to do bovine genetics in Holland, which regards its dairy industry as vital. Initially it was hard to do biotechnology in Germany because of its unfortunate history of eugenics, but over time, Germany seems to have turned a corner insofar as pharmaceutical applications of biotechnology are concerned. Some companies go so far--as Geron has done--as creating their own ethics advisory board to sensitize them to issues surrounding controversial subjects, to coordinate with university-based collaborators, to advise on clinical affairs.

Hughes: Who sits on the Geron ethics advisory board?

Kiley: That board is composed of outsiders--scientists, members of the public, leading ethicists. It mirrors in some respects the national ethics advisory board created by President Clinton several years ago to look at a host of issues in biotechnology, embryonic stem cells being one of them.

Hughes: What is the burden of the committee?

Kiley: To examine the science proposed to be done by Geron and its collaborators, to express its opinions concerning it, to make those opinions known to the public.

Hughes: Does it have the authority to reorient a line of research?

Kiley: No, it does not. I think that would be an abnegation of the fiduciary responsibilities of the board of directors to the shareholders.

Hughes: So it is solely an advisory committee?

Kiley: It is. But it would be unfortunate if the company were to be seen as going against the advice of the advisory committee.

Hughes: Right.

Kiley: These questions are not free from difficulty. We can use the advice. And we do use it. [tape interruption]

Pharmacyclics

Hughes: All right, the next company chronologically that I'm aware of is Pharmacyclics. Please tell me a bit about that.

Kiley: Pharmacyclics is one of my favorite companies. Like CellPro, it was begun in a university setting around the technology of Dr. Jonathan Sessler of the University of Texas at Austin. Sessler had encountered Dr. Richard Miller when Miller was an oncologist at Stanford University and Sessler was a graduate student. Miller earlier had been a co-founder of CellPro and of Idec, the latter a San Diego company which has risen to fame in collaboration with Genentech on a treatment for B-cell lymphoma. Sessler knew that Miller was a company-starter, was grateful to him for having cured him of the lymphoma which befell him while at Stanford, and so approached Miller. Miller got in touch with the people at Kleiner Perkins, who asked me to accompany Miller and Joe Lacob to the University of Texas to negotiate on the Sessler technology.

Sessler is an organic chemist. He did postdoctoral work in the laboratory of a French Nobel Laureate dealing with heterocyclic ring compounds. And what Sessler had done at the University of Texas was to make some large versions of these. They were porphyrin-like molecules. Porphyrins are ring structures made in nature that trap metals within their ring-like structure, a process called chelation, after the Greek "chela," the claw. The Sessler-expanded

porphyrins were large enough to trap very large metallic elements, like europium, lutetium, gadolinium.

In the body, porphyrins are used in energy transfer; the heme in hemoglobin chelates copper. Vitamin B-12 is a porphyrin. Chlorophyll is a porphyrin and is involved in the transfer of energy from the sun to the plant. In magnetic resonance imaging, gadolinium is used to fashion images from incident radiation. And the Sessler porphyrins could be used as MRI imaging agents, for example, to visualize tumors in patients. It also turns out that when they're excited by red light, they kill cells that have absorbed them. That is so when the metal is lutetium. When the metal is gadolinium and they're excited by x-rays, they can increase the killing effect of the radiation.

Porphyrins are often associated with cholesterol. Cholesterol is a key ingredient in building cell membranes. Wherever cells are growing rapidly, a lot of cholesterol is found, and a lot of porphyrins are found in association with the cholesterol. Porphyrin compounds tend to localize in atherosclerotic plaque (which has a substantial cholesterol component) and in rapidly dividing cells in cancer patients where cell membranes are being rapidly constructed.

So now you have a family of agents that find their way selectively to the parts of the body we want most to treat in cardiovascular and cancer diseases; and whose mechanism of action permits diseased cells and diseased tissue to be eradicated by radiation. Using Sessler's compounds, Pharmacyclics has been able to advance to phase III clinical trials with one agent in the treatment of metastatic brain cancer. It's begun clinical trials on primary brain cancer. It's in phase II testing with a lutetium product for recurrent chest wall disease in breast cancer. It's in phase II clinical testing with Alcon, of another agent excited by red light for the treatment of advanced macular degeneration. It's now in the clinic at Stanford and elsewhere with light-activated agents to treat peripheral arterial disease and coronary artery disease. Here the agent is given and then a side-firing red light fiberoptic catheter is intruded into the vessel to activate the material.

I was involved with Pharmacyclics from the start and served it as a director for about eight years until approximately 1998. I think it's just a wonderful technology platform--one body of science that has got a multitude of applications in very important diseases.

Hughes: How and why did you become associated with the company?

Kiley: Well, first my role was to first negotiate the terms under which the Sessler technology would be acquired from the University of Texas. Subsequently, as in so many of the companies I've been involved in, to exercise some oversight in respect of patent strategies and to participate in negotiations with companies, principally those elsewhere in the world, that have taken licenses under Pharmacyclic's technology. Pharmacyclics is regarded as a biotechnology company only in the sense that it's a development-stage pharmaceutical company. But the technology it's applying is more reminiscent of the classic pharmaceutical industry that proceeds from first class organic chemistry.

Defining a Biotechnology Company

Hughes: What in your mind are the defining characteristics of a biotechnology company?

Kiley: I've always thought of a biotechnology company as an organization engaged in becoming a pharmaceutical company, using as leverage for that purpose a fine grip on the powerful new technologies arising around recombinant DNA, genome sequencing, monoclonal and polyclonal antibody production, transgenics--the "new, new life sciences."

More recently, successful companies seem to have been built not with a view to becoming fully integrated pharmaceutical companies, but rather to serve such companies in such things as genomics, target identification, elucidation of disease pathways for intelligent intervention, and so on. And those companies range from the Millennium Pharmaceuticals to the Incyte Genomics to the Celeras of the world, although even some of those are now beginning to take products into the clinic for their own account. I think there's been a remarkable sea change in the pharmaceutical industry over the last several decades from which has arisen a new symbiosis of entrepreneurial companies on the one hand and global pharmaceutical companies on the other.

Hughes: Do you want to observe on the possible ramifications of that condensation?

Kiley: I don't know that I'm any more qualified than anyone else to do that. It is clear that the symbiosis has been productive. For a long time the pharmaceutical industry resembled nothing so much as a wildcatting operation in which discovery proceeded largely by serendipity. Now the new understanding we have of body processes lets us target disease in an intelligent way. At Genentech, for one annual report, we devised the term "the new era of molecular medicine." That connoted intervention in disease at the level at which it occurs, with an understanding of why it's occurring. It's very rare these days for any pharmaceutical company to undertake investment in clinical research unless the mechanism of action of the drug candidate is known at the molecular level. I think biotechnology has brought us to that point.

Choosing Biotechnology to Make Drugs

Hughes: Was it true of biotechnology from the start that an understanding of the mechanism was at the basis of the proposed drug?

Kiley: No. At least from Genentech's perspective, biotechnology began as a cheaper, better way to make protein pharmaceuticals which previously had been extracted from tissue--to make growth hormone in fermentation tanks rather than extract it from pituitaries; insulin in fermentation tanks rather than extract it from animal pancreases, and so on.

Hughes: But was it honestly true that in the beginning it was cheaper?

Kiley: I'm not sure cheap is the right word. The growth hormone market was underserved because of a scarcity of the raw materials from which the growth hormone could be gotten. Later those

raw materials became suspect because of the Kreuzfeld-Jacob syndrome that could be passed from the donor tissue into the patient. In the insulin case, some diabetics had allergic reactions to animal-derived insulin. Diabetic populations were growing. Lilly had to make decisions about building new plants. Should it build a plant to extract animal insulin from pigs and cows whose population growth wasn't keeping up with the growth of diabetics, or should it re-tool itself for an endless supply of insulin made by recombinant DNA? In one case [growth hormone], recombinant DNA led to sufficient product where there was insufficient supply, and the other [insulin], it led to a better product not tied to farm economics.

It turns out that gene-splicing and related techniques are every bit as important as a tool kit for picking apart the mechanism of disease as they are for making protein pharmaceuticals. Indeed at the end of the day, their most important role will lie in identifying targets that can be attacked, not with protein pharmaceuticals, but with classic organic chemicals--pills that you swallow rather than protein you inject.

Hughes: Because of the ease of delivery?

Kiley: No, because one can use the new biology to find out at the molecular level what's wrong and then provide an agonist or an antagonist that can be absorbed through the gut and so taken as a pill in order to interfere at the active site of disease. A great drawback of protein pharmaceuticals is that they can't be taken orally. Recently a number of companies have begun to develop inhalants for such things as insulin. But for the longest time, protein pharmaceuticals were disfavored because people don't like needles.

Geron

Hughes: It was, I believe, a connection with the scientist Mike West that got you involved with Geron.

Kiley: Actually it was--

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Kiley: --Alex Barkas, a partner at Kleiner Perkins at the time, who introduced me to Mike West. Mike founded Geron around work he had done with colleagues, again at the University of Texas, dealing with an enzyme called telomerase. I think the telomerase story is a fascinating one.

West was interested in why we age. He and his colleagues at the University of Texas, where he was obtaining his Ph.D., were studying this enzyme, which in some cells is present in order to repair the frayed ends of chromosomes. It turns out chromosomes have at their tips a long series of repeat sequences that are nature's clock. Every time cells divide, these sequences get frayed. They burn down, if you will, like little fuses until after eighty or so cell divisions, the cells senesce. That happens because telomerase is not present. In cells where telomerase is present, largely in cancer cells, the enzyme repairs the chromosome after cell division, and the cell is effectively immortal.

So West's interest was in proving out the connection between aging and telomere shortening and in finding an inhibitor for telomerase that might be a silver bullet for cancer. Here you have a target present largely only in cancer cells, present in virtually all of them, present in very few normal healthy cells, so a single agent that inhibited telomerase might make the cancer cells mortal with little or no adverse effect on normal healthy cells. The flip side is that if you could find a way to activate in healthy cells the inactive telomerase gene, then you could make those immortal. A very big vision.

Geron was formed around that vision, venture-capital financed. In time it became a publicly traded company. It has worked with Pharmacia and Upjohn and still to this day with Kyowa Hakko of Japan, seeking an inhibitor for telomerase. It's identified a number of promising candidates and one hopes before long it will declare a lead and take it into the clinic for cancer treatment.

Along the way the company has added some other equally fascinating legs to its technology platform. It supported work at Johns Hopkins University and University of Wisconsin that led to the first-ever isolation of embryonic stem cells and embryonic germ cells. These are single cells from which not just the blood system can be derived as in the CellPro case but indeed from which every tissue of the body derives. And the company is now using these in efforts to create, for transplant and other purposes, tissues of various kinds.

We can grow stem cells then set about learning how to control their differentiation so we can guide them in a desired direction. Today Geron has succeeded in making from stem cells beating myocardial cells; it's made liver cells; it's made several types of neural cells and we can equip them with telomerase to grow them copiously without hitting the replicative limit that plagues other attempts to make large populations of cells. One holds out hope that in the fullness of time, we'll be able to grow whole new organs from a patient's own tissue.

Now, the use of embryonic stem cells is not without controversy because they originate from embryonic cells that would otherwise be discarded in the course of in vitro fertilization. Geron has been a leading factor in ethical debates over that question, and with its university collaborators operating with Geron rather than government funding, has become nearly the sole source for the provision of such cells to academic and other workers, even to federal workers who presently are prohibited from spending federal money to generate embryonic stem cells.

Hughes: Does that imply that Geron has given the material?

Kiley: Federally funded investigators are presently permitted to use them if they're acquired other than from government sources, and Geron and its university collaborators are providing them to laboratories all around the world to advance their study.

The company has hedged, if you will, its embryonic stem cell bet by acquiring a third leg to its technology platform, and that is the technology that gave us Dolly, the cloned sheep. Several years ago Geron bought that technology from Ian Wilmut's Roslyn Medical Institute, associated with the University of Edinburgh, and continues to this day to fund work in Wilmut's laboratory, investigating the applications of what is called nuclear transfer in which the DNA content of one cell is placed into a donor egg and cloning achieved in that way, even reprogramming adult cells to become stem cells.

So here is a company not older than about eight years that has brought within its compass three of the most remarkable technologies in the world of biotechnology. It's creating a whole new field we refer to as regenerative medicine and on the side hoping for a silver bullet for cancer and a veritable fountain of youth as well.

Hughes: [laughs] Too bad it's not ambitious.

Kiley: Too bad it doesn't have more money to chase all of these big opportunities.

Kiley's Advice in Patenting and Partnering

Hughes: Tom, go into a bit more detail about what you actually do for these companies, or does is vary a great deal from one to the other?

Kiley: It does vary a great deal from one to the other. I think what I have to offer has a limited lifetime in this sense--two things are very important to start up biotechnology companies: patents and partnering. My Genentech experience was patents and partnering, and I'm regarded as having some competence in those fields. In the earliest days of the company, I can play a great role in those areas but as companies mature, they hire legal departments, they bring in vice presidents for business development, corporate development. And while I can be a very proactive director in the building stages of those companies, the time is going to come when my role is reduced toward mere board participation. When companies move from the business development marketplace and the laboratory bench into the clinic and toward pharmaceutical production, sales, and marketing, my skill set becomes less critical, and those companies are better advised to bring onto their boards of directors people who have been around those tracks. Often at those stages I find myself recycling into earlier-stage companies.

Hughes: That's a self-generated change?

Kiley: Almost invariably, but not entirely so.

I also find myself leaving boards when companies I serve in that capacity are acquired by others. It's not uncommon in those cases for management members to go along and join the board of a larger company, but for the company to shed its venture capitalists and other kibbitzers as it's absorbed into a larger company. That happened in the case of Elan. It happened when CardioGenesis of which I was a director merged with Eclipse Surgical Systems. I left the board of GenPharm when it was acquired by Medarex. I left the board of Synteni when it was acquired by Incyte Pharmaceuticals, and so on.

Synteni and Affymetrix

Kiley: Now, Synteni was an interesting company. It was formed around a Ph.D. thesis. A very bright young man named Dari Shalon, an Israeli émigré, was studying at Stanford a curriculum of his

own design, merging biology and engineering in a way that suited him for instrument design. Dari was interested in following the expression of proteins from DNA by florescence detection. To do that well you have to look at a lot of DNAs at one time. He wanted to make what are now called DNA microarrays. DNA microarray can be thought of as a plate with thousands of deposits of individual DNAs that can detect the corresponding RNAs and yield information about the level of RNA production in particular cells.

Dari was sitting at his desk at Stanford, tapping his pen on a table, frustrated at the difficulty in creating these arrays. One of the attempts he had made involved threads that were steeped in DNA and then woven into a cord that could be embedded in paraffin and then sliced to create an array of DNA dots, if you will. As he sat there tapping his pen, it occurred to him that he could make a pen and print DNA onto chips. He designed a device that could do that, and before long had created, again with Kleiner Perkins' help, a company here in the Bay Area he called Synteni In time, Synteni would put as many as 10,000 genes on a single chip.

Well, as we had moved from gene sequencing to trying to assign function to genes, understanding what RNAs are being expressed either from an embryonic development standpoint or a standpoint or in comparing young to old subjects or healthy to diseased subjects can all be very important, and DNA microarrays are a powerful tool for doing that. I joined the board at Brook Byer's request and served with him. He was chairman. As usual, my principal occupation lay in looking at the patents that emerged from Dari Shalon's work at Stanford, dealing with the license agreement between Synteni and Stanford and also looking over the shoulder at third-party patents.

Before Synteni was formed, Alejandro Zaffaroni created a company called Affymetrix. Affymetrix was also interested in DNA microarrays, but it approached them in a very different way. Its idea was to use semiconductor technologies to build out DNA molecules nucleotide by nucleotide at discrete locations on electrically activated chips. Affymetrix had a very fine patent attorney by the name of Bill Smith [of Townsend, Townsend, and Cres] who claims to have persuaded the Patent Office to give Affymetrix patent claims that cover DNA chips of a certain density without regard to the way in which they're made. And a time came when Mr. Smith and Affymetrix could be heard to say that Affymetrix patents would dominate Synteni's work.

It was a matter of concern: Affymetrix was a better-funded company. Synteni was small by comparison. Affymetrix had substantial current revenues. It was a public company, and we could see a patent fight looming. Incyte Pharmaceuticals was also pressing into the microarray business. It occurred to us this was becoming an elephant dance and we were a mouse. The founders of Synteni [Dari Shalon and his brother Teddy] decided to climb aboard one of the elephants and sold the company to Incyte Pharmaceuticals. Brook and I concurred and that was done, and within weeks the lawsuit came. Indeed, it came before the shareholders actually approved the transaction. I believe it was Affymetrix's hope the lawsuit would prevent Synteni's acquisition by Incyte, whom Affymetrix feared more than Synteni itself. In the event it didn't. The lawsuit is still pending. I read the other day the court has now construed the Affymetrix patent claims more narrowly than Affymetrix would prefer and perhaps to the point of freeing Incyte to use more fully the Synteni technology. That was my only essay of any significance into the genome business other than in connection with some public service in respect to gene patenting and so on.

Hughes: Does that reflect a policy on your part?

Kiley: No, it is simply a question of happenstance. I have invested in companies that are doing genome work but haven't come to join any boards. I was approached some years ago by an emissary [Paul DeStefano]of Human Genome Sciences who were interested in my joining their board. I had just published in *Science* an attack on the NIH patent filings in which Craig Venter's group sought to obtain patents on literally thousands of genes of suspect utility, based on the possession of only partial sequence information. I thought it would be hypocritical to join the board of a company proposing to do the very same thing in the very same week in which this attack on the practice was being published. I said so to DeStefano, a one-time Genentech lawyer who was then in a private law firm representing HGSI. He said he had communicated my concerns to Wally Steinberg of Healthcare Ventures who had formed HGSI, and he reported Steinberg wasn't put off by the inconsistency. But my fear was that it would confirm what everybody thinks about lawyers anyway, so I foolishly said no and probably cost myself a lot of money as a result.

Hughes: I notice that in several of these instances Brook Byers seems to have been the instigator for getting you involved. Why is that?

Kiley: I wouldn't read too much into that. Venture capitalists are very good at leveraging their people resources by getting other people to help their companies in return for stock compensation. I've got the greatest respect for Kleiner Perkins, and for Brook and Joe Lacob in particular, for their contributions to biotechnology--Alexander Barkas, as well, formerly at KPCB and now at Prospect Ventures. But I've also worked in other companies at the instance of other venture groups, ranging from the Mayfield Fund to Institutional Venture Partners.

More on Kiley's Expertise

Hughes: Is the attribute that they're most interested in acquiring through you your intellectual property expertise?

Kiley: At the outset I think it was patents. It later became patents and partnering. Having now been on boards of directors for thirteen or fourteen or fifteen years, commencing with Genencor while in house at Genentech, I suppose like anybody that has seen a lot of companies go through their birth pangs, I've learned something about what's good to do and what's good to avoid, but the world is full of people who can do that.

Hughes: I would think that the particular constellation of experience and training that you have is not easily duplicable.

Kiley: I've certainly been at it longer than most patent attorneys. I have seen a range of companies. Perhaps it's a case of jack-of-all-trades and master of none. There's a certain amount of dilettantism to what I do and real limitation as a result.

Hughes: Well, there's no attorney with the longevity that you have in respect to biotech intellectual property law, is that not true?

Kiley: I think [Bertram] Rowland can claim priority.

Hughes: Because of the Cohen-Boyer patent, right?

Kiley: Other than Bert, I'm hard-pressed.

Hughes: That would have been in 1974, and you became involved in--

Kiley: In '76.

The point I was trying to make, Sally, is that there is no substitute for focus. One person who is devoting sixty hours a week to one job is going to know a lot more about his niche than any member of his board of directors, however experienced. He's going to make a bigger difference in the world than any member of his board of directors. So it's fair to characterize the way I've lived my life since Genentech as quasi-retirement, and I am proud of it. It's a lot of fun, it's financially rewarding, and it leaves me the master of my own calendar. After years of meeting frantic court schedules and sitting in windowless offices at Genentech and looking at the planet from the windows of airplanes and conference rooms, I can do as I wish now. And it turns out, what I wish to do, at least in part, is to stay involved in these exciting young companies because it's so much fun and so enlightening.

Connetics

Hughes: Well, going down the list of companies you have served, I think the last one that you wanted to talk about today is Connetics?

Kiley: Connetics is another company whose founding venture capitalist was Alex Barkas of Kleiner Perkins. I joined the board in the course of its formation partly because it started with a product with which I had some familiarity, that is, a recombinant protein called relaxin. Relaxin was identified some years ago at the Howard Florey Institute in Australia. It is a protein made by women when they are pregnant, and it's involved in remodeling their pelvic structure in preparation for birth. Genentech acquired the product, hoping it could be used to sidestep caesarian sections. It worked very well in chimpanzees and not at all in humans, whereupon Genentech proved willing to license it to a newly formed company wanting to use it for other purposes.

The newly formed company was first called Connective Therapeutics because it proposed to focus in connective tissue disease. It is now called Connetics Corporation.

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Kiley: Scleroderma is a terrible disease that predominantly affects women. It is like slow mummification in which connective tissues of the body darken and harden, feeling is lost. Ultimately many die of respiratory complications. The hope was relaxin could remodel this

tissue and provide the first-ever treatment for the disease. Just recently we broke the code on phase III data and found the product was ineffectual for scleroderma, to our great regret.

Hughes: How could it have gotten that far in the trial system?

Kiley: We're now well outside my area of expertise, but I will say the phase II results were encouraging and probably turned out to be just a placebo effect.

Interestingly, the phase III patients showed some reactions suggesting relaxin could play a role in the treatment of congestive heart failure and kidney disease. The company is now moving with those other indications. It's also looking at relaxin for use in in vitro fertilization because of the effects it has in placental formation. In the meantime it has built itself a profitable business in the dermatology area.

The usual suspects can be found in association with Connetics. One of its founders, Edward Amento, was a Genentech alumnus. Kirk Raab, one-time CEO of Genentech, is a very active chairman of the board on which I sit. There's another Genentech connection--Connetics also licensed from Genentech gamma interferon, which David Goeddel first cloned and I patented. In Genentech's hands gamma interferon found use only in the treatment of an orphan disease, chronic granulotomous disorder, but Connetics thought it would have wider applications. It turns out that it does.

InterMune Pharmaceuticals

Kiley: We spun gamma interferon into another venture-financed company called InterMune Pharmaceuticals. We did it because we wanted to focus on relaxin and the dermatology business. No sooner had we hipped gamma interferon off to InterMune in return for a significant ownership stake than a group in Europe published a double-blind study in which it used gamma interferon to treat patients with pulmonary fibrosis. And by all accounts it worked like a charm. So here is InterMune newly formed and with all rights in the United States to gamma interferon, and into its lap drops statistically significant evidence the product could be used to treat a very large market. InterMune is now a public company and quite valuable, so another Genentech egg has finally hatched, albeit in someone else's nest.

Hughes: There seems to be an element of luck to a lot of this. It's not as though there's a clear path from the lab bench to the supermarket shelf.

Kiley: Well, Louis Pasteur said, "Fortune favors the prepared mind." Scott Harkonnen's mind [CEO of InterMune] was prepared to go from Connetics to do something with gamma interferon when other minds weren't. Bob Swanson always said, "I'd rather be lucky than smart," and until the end he was quite lucky. Somebody was going to pick up gene-splicing and do something with it--someday. Bob was lucky to be looking for something to do when he found Herb Boyer. I doubt it would have been picked up so fast by any other, but it would have come eventually. Sooner or later nature reveals all her secrets. Maybe not all, but at least down to Planck level.

Cardiogenesis

Hughes: What about this coterie of other companies with which you had more glancing connections?

Kiley: I'd be inclined to say not more glancing, but in some respects less interesting from a technology standpoint. Cardiogenesis, now part of Eclipse Surgical Systems, was a medical device company that pioneered transmyocardial revascularization. The notion of TMR, as it's called, is if you punch holes in the heart with a laser, the heart responds to the insult by angiogenesis, and so this can be an adjunct to bypass surgery. And indeed in the clinic we saw significant reduction in anginal pain and improved exercise tolerance as a result of TMR. But for business reasons it proved appropriate to merge Cardiogenesis with another such company, and when that happened, I left the board.

Insite Vision

Kiley: I was a director of Insite Vision for a nmber of years. It's an East Bay company exploiting a technology for ophthalmic drug delivery using a liquid polymer. The polymer is administered as an eye drop and then becomes a depot for drugs to treat various ophthalmic diseases.

Kiley's Current Corporate Affiliations

Kiley: I'm working with some interesting companies these days: Origen Therapeutics where Robert Kay who headed the human antibody mouse project at GenPharm is now proposing to make transgenic chickens as pharmaceutical factories for antibodies and other proteins. I'm working with Mycometrix,[1] a microfluidics or lab-on-a-chip company in somewhat the same space as Caliper or Aclara. But rather than using silicon technology, Mycometrix is exploiting a Caltech technology that involves chips made from the same material as soft contact lenses, so they can be air-actuated. The company is run by a very attractive young entrepreneur [Gajus Worthington] who for fun goes into the wilds of Alaska and builds log cabins with his hands. His vice president for business development [Todd Krueger] just got back from ice-climbing in Patagonia. I get along well with those fellows in view of my own perambulations.

I recently had some interesting adventures in company formation with three faculty members [Drs. Garry Fathman, Paul Wender, and Edward Engleman] of Stanford. We co-founded a company called Cellgate. Cellgate has just attracted $18 million in venture financing from Healthcare Ventures and New Enterprise Associates. Skin exists to keep unnatural molecules out of our body and has been called "the Mount Everest of drug delivery." And we think we've found a way through the skin and will be entering the clinic this year to see if we're right.

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[1]Now by change of name Fluidigm Corporation.

Now I had a less happy experience in company formation with a company called BioWire.com of which I'm also a co-founder. We followed by a year or so a company called Chemdex into the business of supplying biotechnology reagents via the Internet. The Chemdex approach was to rejigger the information infrastructure and purchasing systems of major enterprise clients. Our approach, using viral marketing, was to attack accounts that Chemdex didn't call upon--universities, small companies and so on. And in the end I think our business model made a lot more sense, as we revised it over time, than Chemdex's did. Chemdex in the meantime has lost virtually all its value and the resulting downdraft has made it impossible to continue to finance "B2B" companies like BioWire. So as has happened on a number of other occasions, I managed to sail out of my area of expertise and into troubled waters. You think I would learn. I have been there in virtual reality, I've been there in x-ray technology, now I'm there in e-commerce--and once again I'm getting my head handed to me. But so it goes. You can't make an omelet without breaking eggs. Or perhaps I should say, "If you live by the sword, you die by the sword." In any event, it's been a learning experience, and we are this very day in negotiation to sell BioWire to another company.

Hughes: Do you see this entrepreneurialism going on into the future?

Kiley: It is habit-forming. There are very few people who have succeeded in making two great companies. Jim Clark is one, Vinod Khosla another. I'm sure a half-dozen others could be mentioned. But I certainly have no expectation anything I help to start will ever rival Genentech. That would be asking too much for one life. That doesn't mean there aren't a lot of fascinating technologies out there of potential great utility and a lot of very interesting people trying to make them work. And if I can help them, why, I'm delighted to do it so long as it doesn't take all my time.

Member, Office of Technology Assessment Panel on Patenting

Hughes: Tom, what did you mean by public service in terms of the human genome?

Kiley: I was referring to some non-commercial activities that I got mixed up in. It began with a committee assignment under the Congressional Office of Technology Assessment, that wanted to study controversial aspects of human gene patenting. I served on that committee with some other lawyers, scientists, ethicists, people from divergent backgrounds. We put together a moderately intelligent report which never got printed because Congress in its wisdom eliminated the Office of Technology Assessment along with the budget that was required to print the report.

But it was all worth it because of one experience. And that occurred one day when someone in the committee referred to remarks of Senator Mark Hatfield in the *Congressional Record*, who was outraged at the prospect that human genes would be patented: "Animal genes, okay, but not human genes," he said, "because that's God stuff." And I remember being perplexed how human DNA could be "God stuff" and animal DNA not.

I remarked on my perplexity and Craig Venter, who was a member of the committee and later the founder of Human Genome Sciences and Celera, said, "You know, that's right. After

all, we regularly find in human DNA close homologs to animal DNA." I pointed out that our genetic sequence differs from that of a chimp only by about a percent and a half. Venter again agreed, noting that he had been looking through his human brain cDNA library the other day and had found a sequence identical to one from a blue-green algae. And I was obliged to say: "Tell me, Craig, whose brain was that?" [laughter] A great flurry resulted amongst members of the media. That was lovely.

NIH-DOE Joint Committee on the Human Genome, 1992

Kiley: Well, as a result of that service, Bob Tjian, a fishing acquaintance of mine and a professor here at Berkeley, also a co-founder of Tularik, Dave Goeddel's company, approached me and asked me to come and talk to a committee on which he served. That was the NIH-DOE Joint Committee on the Human Genome. Members of that committee were exercised over the NIH patent filings, which they thought threatened to be obstacles to their use of the basic raw materials of science. I agreed with them and put together a pot-boiler of a little speech. I flew down to San Diego, and sang to the choir, an audience holding upwards of a dozen Nobel Laureates. So the outcome was Paul Berg, a member, asked me to draft a letter opposing the filings, which the committee endorsed and published in *Science*. Yet another call for a moratorium. I later wrote a paper that *Science* published as part of a perspective on the controversy.[1] Bob Tjian looked at this single-authored publication in *Science* and said to me, "Finally, Kiley, you have a CV." [laughs]

Bernadine Healey was then director of the National Institutes of Health, and the scientists of America are her constituency, and the leaders among them were in an uproar about patent filings done by her own agency. She asked Berg to put together a collection of "wise men," as she called them (with remarkable gender insensitivity) and bring them to Washington to advise her how to resolve this dilemma. "Don't bring Kiley," she said, out of fear the presence of a lawyer would feed further controversy. Berg tells me he replied, "He's my lawyer, [laughs] and if he doesn't come, I don't come." So off I went to Bethesda.

We met for breakfast and to get our act together, and there was Mr. Kiley from an undistinguished educational background giving counsel to Nobel laureates such as Dan Nathans, Dave Baltimore, Michael Brown, Joseph Goldstein, Jim Watson, Paul Berg--quite a heady trip and a successful one because in the end, the National Institutes of Health did withdraw its patent applications.

Hughes: What were your arguments?

Kiley: Earlier in these interviews, I've expressed some concern about the proliferation of patenting in biotechnology to the point where a system designed to incent progress in science could become an impediment to its practice. I don't have any substantial objection to patenting products of nature. I have a lot of problems with giving patents to people that confer power all out of

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[1]Thomas D. Kiley, "Patents on Random Complementary DNA Fragments?" *Science* 1992, 257: 915-18.

proportion to their contribution. The notion one could patent a gene and control commerce in its product on the basis of having sequenced a few percent of its DNA and hypothecated some insubstantial utility is just wrong.

I believe NIH thought it was doing the right thing. They had a rather tortured explanation. Harking back to the Bayh-Dole Act, the notion was if you publish the sequence of a DNA, you were publishing the amino acid sequence of the protein it encoded. Having published that without first patenting it made it impossible for others to patent it as a composition of matter. Since there will be no patent, no one will have economic justification for making this into a medicine and bringing it to the public. That was their rationale. "We have to patent these if there are going to be any patents, and then the patents can be used to incent pharmaceutical development."

Well, nice in theory, but the problem is the wrong people wind up holding the patent and simply lie in wait for others to do the hard work. More recently the Patent Office has purported to raise the utility bar. That's a very difficult thing to do, because it's hard to draw bright lines between the useful and the useless. I think the Patent Office is now also declining to grant patents on incomplete sequences.

Hughes: Is the Patent Office proposing to issue guidelines for this specific purpose?

Kiley: It has done so in recent months. The guidelines are not particularly bright lines. Utility must be substantial, credible, and specific. Now, what do those words mean? Credible, all right, I believe you. Substantial means more than insubstantial, less than nothing, but otherwise sheds little light. And specific is not terribly helpful either, is it? Because an iota can be a specific iota. A scintilla can be a specific scintilla. So we're left with composition of matter patents which cover all uses, justified by little utility at the outset.

Hughes: So these specifications have to be fought out in the courts?

Kiley: It doesn't happen. The courts very seldom get into issues of utility because they suppose the law is that any utility is sufficient. If things were useless, people wouldn't be in court fighting about them. Ergo, the invention must be useful. Thus that requisite of patenting has been satisfied. But is it fair for someone to spring up with a patent gotten because his robot read a couple hundred base pairs, and nothing else was done until another's deep investment led to a clot-busting agent encoded by the whole DNA? The DNA's true utility wasn't known to the patentee, but it's nevertheless useful. The system rewards lucky guesses. It rewards people sometimes over-greatly. [whispers] But I think we're rehashing something we talked about before.

Extracurricular Activities

Kiley: I like to travel and fly-fish and shoot birds and otherwise act in an ungrownup way, and my calendar now permits me to do that. I think I've been to forty or fifty countries since leaving Genentech, often in those pursuits--everywhere from Mongolia to Antarctica to Iceland,

Namibia, Zambia, Zimbabwe, Botswana, South Africa, Kenya, Tanzania, Patagonia, Tierra del Fuego, you name it.

Hughes: Do you see any common thread between your hobbies and your professional life?

Kiley: None at all. I think fishing rods and shotguns are just excuses for being in the big, clean parts of the world where the animals live. And so it's travel more than sport that inspires me, although sport is the excuse for being there. It's a good excuse for not having a job. [tape interruption]

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Kiley: Remarkably for a one-time trial lawyer, I will confess to some embarrassment for having spent so much time talking about myself and my own activities. I don't want to create the impression I have hewn great strokes consistently through my involvement in biotechnology. Rather I would say I have been fortunate in my associations and most fortunate to have met Bob and Herb when I did, and begin this fascinating odyssey. I mentioned earlier, fortune favors the prepared mind, and that Bob Swanson always said he would rather be lucky than smart. Far more so than Bob, I think my own involvement in biotechnology was an exercise in fortune favoring the *unprepared* mind. [laughter] But I'll take it.

Hughes: Very good.

Kiley: Thank you, Sally.

Hughes: And I thank you.

Transcribed by Amelia Archer
Final typed by Kathleen Zvanovec-Higbee

TAPE GUIDE--Thomas D. Kiley

APPENDICES

Thomas D. Kiley

Biographical Information--October 2002

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1988-present Corporate Director and Consultant

Presently member of the Board of Directors of Connetics, Inc. (CNCT), Geron Inc. (GERN) and CellGate Inc. (co-founder), a private company.

Previously a director of:

Athena Neurosciences Inc. (acquired by Elan Pharmaceuticals, Inc.)
Biowire.com, Inc. (chairman, cofounder) (asset sale, Lab Velocity, Inc.)
Cardiogenesis, Inc. (acquired by Eclipse Surgical Systems, Inc.)
CellPro, Inc. (asset sale, VimRx, Inc.)
Crystallume, Inc. (acquired by Electronic Design, Inc.)
GenPharm International, Inc. (acquired by Medarex Pharmaceuticals, Inc.)
FailSafe Technologies, Inc.
Glycogen, Inc. (acquired by Cytel Corporation)
InSite Vision, Inc.
New Leaf Systems, Inc.
Pharmacyclics, Inc.
Signition, Inc.
Sosei, Ltd.
Synteni, Inc. (acquired by Incyte Pharmaceuticals, Inc.)
V-Ray, Inc.

1980-1988 Genentech, Inc., South San Francisco, CA

Variously vice-president and general counsel and vice-president for corporate development.

Negotiated Genentech arrangements with KabiVitrum, Eli Lilly, Hoffman La Roche, International Minerals and Chemicals, Ciba-Geigy, Monsanto, Kyowa Hakko, Mitsubishi Chemicals, Boehringer Ingleheim, Daichi Seiyaku, Toray Industries, Institute Merieux, Chemie Grunenthal, Bayer.

Director of Genencor, Inc., a Genentech-Corning Glass joint venture, and of H.P. Genenchem, a Genentech-Hewlett Packard joint venture.

1969-1980 Lyon & Lyon, attorneys, Los Angeles, CA

Associate (1969-1975), partner (1975-1980), intellectual property and related litigation Represented Genentech, Inc. from inception in 1976.

Authored Genentech's brief *amicus curiae* in Diamond vs Chakrabarty, 447 U.S.303 (1980).

1967-1969 E. I. duPont de Nemours & Co., Inc., Washington D.C.

Patent solicitor, Elastomer Chemicals Department.

1965-1967United States Patent and Trademark Office, Washington, D.C.

Patent Examiner, Group 171.

Education

B. S. (Chemical Engineering) The Pennsylvania State University 1965; J.D. with highest honors, George Washington University Law School 1969, law review editor.

Publications

The National Law Journal, October 11, 1993 at S14 (impact of biotechnology of health care reform).

"Patents on Random Complementary DNA Fragments," Science 257, 915-918 (1992).

"Negotiating Royalty and Related Features of Technology Transactions," in The Art of Negotiation and Reconciliation, A.I.P.L.A. Thirteenth Annual Institute, Palm Desert, CA, January 31-February 3 (audiocassettes).

"Licensing Revenue for Universities: Impediments and Possibilities," Ch. 7 in Partners in the Research Enterprise, T.W. Langfitt et al, eds, University of Pennsylvania Press, Philadelphia, PA (1982).

Speculations on Proprietary Rights and Biotechnology," in Banbury Report 10. Patenting of Life Forms, Cold Spring Harbor Laboratory (1982).

"Trade Secrets and Biotechnology" in Protecting Trade Secrets, Course Handbook 131, Patent, Copyrights, Trademarks and Literary Property, Practicing Law Institute (1981).

"Patent and Political Shockwaves of the Biological Explosion," Proceedings of the Southwestern Legal Foundation Patent Law 17th Annual, Matthew Bender, publ. (1979).

"Learning to Live with the Living Invention," 7 American Patent Law Association Quarterly Journal 220 (1979).

"Common Sense and the Uncommon Bacterium—Is 'Life' Patentable?" 60 Journal of the Patent Office Society 468 (July 1978).

"Eliciting Patent Examiner Testimony," 59 Journal of the Patent Office Society 629 (October 1977).

Past Service

Member of the Study Committee of the Children's Vaccine Initiative (Institute of Medicine).

Member of the Advisory Panel, U.S. Congress Office of Technology Assessment Study on Human Genome patenting.

Chair, Special Committee on Microorganism Patenting of the Intellectual Property Law Section of the American Bar Association.

Intellectual property consultant to the NIH-DOE joint committee on the human genome and to the Director of the National Institutes of Health in the same regard.

Member of the Board of Directors, Los Angeles Intellectual Property Law Association.

Vice-chairman of the Federal Practice Committee of the American Intellectual Property Law Association.

Interrogator, oral history project of the Ninth Judicial Circuit Historical Society and of the University of California at Berkeley Bancroft Library's project for the oral history of the birth of biotechnology.

Member of the Board of Trustees of The Crystal Springs-Uplands School, Hillsborough CA.

Addresses

Invited talks at Stanford University School of Business; Stanford University School of Law; UC Santa Cruz; UC San Francisco; UC San Diego; University of Santa Clara School of Law; University of Pennsylvania; Dickinson College and Dickinson School of Law; Whittier College; Banbury Center of Cold Spring Harbor Laboratories; European Center for Management in Brussels, Belgium; University of Western Australia; Southwestern Legal Foundation; Practising Law Institute seminars in New York, San Francisco and Los Angeles; Cowen Annual Conference on the Pharmaceutical Industry; at annual meeting of the American Bar association, Section of Patent, trademark and Copyright Law; to Intellectual Property Law Associations of San Francisco, San Francisco Peninsula, Orange County and Los Angeles: California Inns of Court Society; Bay Area Business Development Roundtable; Program Advisory Committee on the Human Genome; Bay Area Bioscience Center; annual meetings of the Union Internationale des Avocats, of the Drug Discovery Section of the Pharmaceutical Manufacturers Association, of The American Economics Association and of the Licensing Executives Society; Commerce Secretary Brown's 1993 Technology Summit; inaugural Medical Device CEO's Summit; inauguration of the Annual Katz-Kiley Lectures at The University of Houston Law Center;

Cal/Bio Summit '95; UC Berkeley Haas School of Business Symposium on R&D Investment and Economic growth in the Twentieth Century; V^2 CEO Forum 2002.

Personal

Married 34 years, 3 children.

(L) Bob Swanson, former venture capitalist, two years after founding Genentech and the biotechnology industry.

(R) Alison Kiley, twenty-three years before becoming a venture capitalist (Alta Partners).

(slightly crazed Polaroid photograph, circa 1976)

APPENDIX C

PATENT AND POLITICAL SHOCKWAVES OF THE BIOLOGICAL EXPLOSION

(Address to the San Francisco Patent Law Association, January 12, 1979)

Ladies and Gentlemen:

If the ambitious title of my address this afternoon proved half as persuasive in bringing you here as was the lure of alcoholic refreshment, then it will have served its purpose. I can accordingly discard it, and discuss with you only those things that time permits. "Mind-boggling" is too conservative a term for the recent revolution in biology, and it would take hours to even approach a comprehensive listing of the subjects it has impacted. They include at least the freedom of scientific inquiry, its proper limits, what some interpret as a rising tide of anti-intellectualism, ethics and other philosophies, medicine, ecology, agriculture, even communications technology -- and, of course, those old stand-bys of cocktail conversation: religion, law, politics, and sex.

Those here who know me will have predicted that the last will be first in the order of my discussion. They will have predicted that I could not resist injecting sex into biology, nor blending impropriety and proprietary information.

The sad fact is that I cannot do this. Indeed, within my time constraints, I have but a moment or two to explain to you how the most elaborate genetic engineering can be done in the laboratory. I will begin now.

This (indicating) is the world's largest chromosome. It is an elephant chromosome, and I will say it was extracted only with the greatest labor by a daredevil team of genetic engineers, operating south of the Kalahari desert.

It is very little different from our own chromosomes, except for a small percentage that encodes the information for a mammal that is "elephant" instead of "man," and that walks on four legs instead of two.

In one sense, it is very little different from dictaphone tape. Like such tape, it contains millions of bits of information that can be transcribed by suitable machinery. You can run this gob of DNA through cellular machinery, transcribe and translate it, and your output is more "Elephant." In the process of transcription, machinery just like the heads of a playback recorder run along these strands and interpret their information. The endproduct of dictaphone transcription is typescript. In the case of the chromosome, it is protein.

Now, everyone knows that its easy to determine the sex of a chromosome. Just ask it to pull down its genes! In fact, this gob in my hand is the DNA of a <u>female elephant</u>, as witness this little loop of DNA I have just extracted from it.

As it happens, before I got this gene the genetic engineers gave the little lady some new information. What they did was this:

First, using some enzymatic scissors, they snipped open the little loop (we call it a plasmid). Next they stitched in a new gene -- one actually made in a test tube. I'm talking about these little yellow and white strips you see in the plasmid.

This reengineered plasmid has an interesting property. You don't have to put it back in the elephant to get it to work. We couldn't do that if we wanted to. But you can put it into a bacterial cell, and you can use the machinery of the cell to make the new protein called for by the synthetic gene. I'll do that right now.

This (indicating) is the world's largest bacterial cell. I've put the plasmid into it, and now we'll find out what marvels the geneticists have planned for us. Hold onto your hats....

(sultry, elephantine voice:)

"Hello. I am the promotor for this gene. Begin on my signal transcription of the new gene for blond hair and two big, beautiful...tusks? Begin!" (sound resembling typing...).

Ladies and Gentlemen, most people do not think these new tools are funny. I do not. But for good or ill, we have

them. We can't make blond elephants or ladies with big tusks, but we do have an opportunity to do much that will benefit mankind. That opportunity has not come unattended by controversy.

In large part, the controversy has been fueled by the perception in several quarters that gene splicing is biohazardous, and proponents of that viewpoint have devised numerous scenarios whose common conclusion can be simply stated: "If our reach far exceeds our perception of its consequences the results could be disastrous." At least one critic has said that if we use this new technology, "the future will curse us for it." One result pertinent to the intellectual property area has been the birth of numerous proposals for preclearance of proposed experimentation by governmental or other bodies, with obvious consequences for trade secrets, preservation of foreign patent rights and the like. On another front, the new techniques have lent momentum to a patent law question which in fact goes well beyond them. I refer to the question whether new life-forms can, or should be, patented. This patent law question, of course, involves not only the products of the new gene-splicing technology but also other novel organisms gotten in more traditional ways. Before discussing these topics in detail, however, I would like to turn to the broader controversy because it affords a microcosmic view of the

manner in which society responds to profound technological challenges. That is a view which should be of significance to us, because our profession puts us at the cutting edge of new technology and requires that we consider and interpret, virtually on a daily basis, the meaningfulness of new technological developments to our society.

To give you some understanding of the larger controversy, I must first tell you some thing of its history.

Twenty-five years ago, Watson and Crick first described for us the chemical nature of what is virtually the stuff of life, DNA. In the ensuing years, molecular biologists deciphered the genetic code, learning how information encoded in DNA is unraveled into the things that make us what we are. In 1973 this research began to assume terrific momentum, when California scientists came upon tools that permitted actual manipulation of DNA, even to the point of snipping it apart and rearranging it. As proposals for further research in the field began to be aired, some scientists expressed concern over the ecological consequences of those proposals, not least of which involved cancer studies that would entail implantation of genetic information from a virus associated with cancer into a bacterium that is a common inhabitant of the human gut. The result was a

virtually unprecedented call among scientists for a moratorium on gene-splicing experiments, until the implications of such experimentation could be discussed at an international conference. In February 1975 that conference, attended by scientists from all over the world, was held at the Asilomar Conference Center here in California. What emerged from Asilomar, after sometimes furious debate, were proposals for various levels of biological and physical containment, depending upon the perceived danger of particular levels of experimentation. With some refinements, these were ultimately adopted by the National Institutes of Health of the Department of Health, Education and Welfare. As adopted by NIH, the Guidelines for Recombinant DNA experimentation would apply only to those conducting research with government funding.

As the NIH Guidelines were nearing completion, the controversy spread to Massachusetts, resulting in a classic confrontation between Town and Gown. Cambridge city officials expressed dismay at proposals for Recombinant DNA research in Harvard facilities, demanding a full disclosure and public debate over the nature of that experimentation in advance of its implementation. Cambridge, of course, is represented in the United States Senate by Ted Kennedy, whose interest in health-related issues had been well-developed by that time.

Before long, Sen. Kennedy was championing a call for regulatory legislation at the federal level, which would extend identical controls both to those doing government funded research, and those engaged in privately funded work.

A number of the proposals for legislation embodied a variant on the notion that "war is too serious to be left to the generals." These would have provided for bodies composed of a majority of non-scientists to pass on the safety of proposed experiments. Others would institute local "biohazard committees" in which knowledgeable scientists would predominate, which would be required to clear experiments before they could be performed. The proposals included stiff penalties, both civil and criminal, for violation of the regulations and on occasion, as in legislation introduced here in California, those who propose to conduct such research would be subject to standards of strict liability in the event of consequent injury.

One question that came quickly to the fore involved notions of federal pre-emption. Should a patchwork quilt of regulation hamper science, or should a single, uniform federal standard be applied? Could more stringent local standards supplant the federal regulatory process, substituting local community standards for a national view embodied in federal legislation, more or less as has been done in the case of obscenity? Flavoring debate over those questions was the

indisputable fact that microorganisms do not respect political boundaries, as witness the recent outbreak in this country of Russian flu.

As the debate wore on, other quarters were heard from. Civil libertarians found a parallel between freedom of expression and freedom of inquiry, arguing a first-amendment freedom to conduct basic research. As might be expected, the Friends of the Earth, the Sierra Club and other like-minded bodies contributed their own viewpoints. And in the District of Columbia, action was initiated against the Department of Health, Education and Welfare to enjoin risk-assessment experimentation underway at the Government's Fort Detrick, Maryland facility.

In the midst of this, the Patent Office made its own timorous contribution. According to a Commissioner's notice, and to encourage the rapid dissementation of information in this important field, the Patent Office would expedite the examination of applications relating to DNA research, upon the applicant's undertaking to abide by the NIH Guidelines. That salutary action, ultimately approved in principle by the Government's own inter-agency committee on Recombinant DNA research, was nevertheless promptly withdrawn when the Commissioner came under fire from HEW. In fact, at present

the Patent Office has suspended examination of many applications in the field, although for an unrelated reason. Pending resolution of the question whether living organisms can be patented, applications containing such organisms are to be held in abeyance.

Although as they then stood and, indeed, as things presently stand, the NIH Guidelines extended only to Government-funded research, industry was quick to offer voluntary compliance with the NIH Guidelines for further experimentation, while voicing concern over so much of those Guidelines as would require disclosure in derogation of trade secrecy. Some politicians were taking a different view. For example, in introducing his own legislation, we heard this from Senator Dale Bumpers of Arkansas: "I am saying we are in a field which is entirely too dangerous to worry about proprietary information."

~~Now, industry's concern over the proprietary nature of its own research efforts was understandable~~. Better-reasoned legislation ~~nevertheless~~ provided that information supplied for biohazard review would be subject to the Freedom of Information Act, unless it fell within that Act's exemptions for "trade secrets." Those exemptions offer little comfort, in the view of many commentators. First, we are all familiar with the difficulty of demonstrating what is and is not "trade secret." It is a little bit like shoveling smoke.

Imagine the difficulties one would encounter if advised that proprietary information will be published unless within 10 days an agency can be persuaded that it is in fact trade secret. Imagine further the difficulty in persuading a federal court that an adverse agency decision is unsupported by substantial evidence, and succeeding in your persuasion in advance of agency publication! And consider those difficulties against a backdrop that includes publication in the Federal Register of your proposed course of experimentation unless the trade secret "exemption" can be made out.

What is more, it is not altogether clear that the trade secret "exemption" to the Freedom of Information Act is effacious. It is well documented that fully ninety per cent of the FOIA requests to the FDA are initiated by companies boldly attempting to eke out their competitor's trade secret information -- more or less federally legitimatized industrial espionage. And ~~it is not at all clear that trade secret information information is truly exempt.~~ The legislative history of the FOIA can be interpreted to suggest that the trade secret and other exemptions are only permissive, and merely mark the outer limits of information that may be withheld by the agency. In other words, invocation by the agency of the exemption may be optional. And one cannot expect an agency to whom such a request is addressed to vigorously enforce another's trade

secret right, when in effect the request puts the agency in the unhappy situation of being sued by one party if it discloses, and by another if it does not. This is particularly so where Courts place the burden of demonstrating the trade secret character of the information on the agency itself, as occurred in the Washington Research Project litigation [Washington Research Project, Inc. v. Department of Health, Education & Welfare, 504 F.2d 238 (D.C. 1974)] and it is yet not clear that local biohazard committes would be immune from the operation of the Freedom of Information Act, to the extent they stand in the shoes of Government and issue final opinions discoverable in the hands of a Government Agency under that Act. Cf. The Renegotiation Board v. Grumman Aircraft Engineering Corp., 421 U.S. 168 (1975).

Some have suggested that private industry could withhold proprietary information pending the submission of a patent application. Once such an application had been filed, industry would be required to trot out its experimental records to demonstrate compliance with NIH Guidelines, with denial of a patent as the sanction for revealed failure to so comply. I expect this proposal will die aborning. Others have proposed that specified categories of information be specifically exempted from disclosure under 5 U.S.C. 552(b)(3). None of the bills I have seen adopt this proposal.

In summary, on the trade secret side, I think that if legislation is adopted, Congress will pay heed to the need for confidentiality under appropriate circumstances. In fact, the technology is not at all "so dangerous that we can't worry about proprietary information." On the other hand, I expect that the best one can hope for is conventional treatment under the trade secret exemption of the Freedom of Information Act where third-parties seek competitive information, and the usual burden of persuasion where agencies determine on their own initiative that information before them is appropriate for publication.

Now, a number of Bills died with adjournment of the Ninety-Fifth Congress, ~~and~~ it remains questionable whether legislation in this area will emerge from the Ninety-Sixth Congress. Many of the same scientists who, by their own expression of concern, initiated a prairie fire of legislative activity and public debate now caution restraint in regulating basic and, indeed, applied research in the field. Since the onset of the debate, much evidence has come into hand to suggest that earlier disaster scenarios were, to say the least, exaggerated. Many of the same researchers who first cried "wolf!" now express the view that work in this field, if conducted commonsensically, presents virtually no prospect for biohazard. Effective this very month, the National Institutes of Health have

somewhat relaxed the guidelines for research in the field. On industry's part, voluntary compliance with those guidelines appears to be working, allaying the concerns of some legislators. And, while no disaster has befallen us, the benefits of the new technology have come dramatically into view.

As one example, as little as a year ago, a privately-financed Bay Area company announced, for the first time, bacterial production of a human brain hormone by a bacterial culture in which synthetic genes had been implanted and then "turned on". More recently, the same company re-engineered other bacteria, turned them on, and produced the component parts of human insulin. ~~In an era of increasing diabetes and diminishing~~ sources of animal-derived insulin, the significance of such accomplishments cannot be overstated, and it may be that the flowering of this science has only begun. Let me give you some examples.

To begin with, there is a substance called Interferon that some speculate may prove to the the "magic bullet" that kills cancer, if it can be economically obtained in sufficient quantity, as by resort to Recombinant DNA technology. Others have proposed resort to that technology for cheap production of antibodies for diagnostic use, a wide variety of other hormones, enzymes with wide-spread industrial applications, and vaccines. Others have proposed

its use to confer on food crops the ability to fix their own nitrogen from the air, eliminating the need for much fertilizer. And as a research tool, the technology bids fair to greatly expand our understanding of how genes regulate themselves, with potential benefits in understanding cancer and many of the fifteen hundred odd genetic diseases that afflict us.

In a free enterprise system, it is likely that much of this work will be privately funded by investors with an eye on the enormous rewards that may come. That raises the question whether advances in this field can be made proprietary, or said another way, whether the patent incentive will foster research in the area. In turn, that may depend on the question whether novel microorganisms can be patented.

A year or so ago, the Court of Customs and Patent Appeals said, "Yes," in two cases which in fact did not involve the new technology, but rather organisms gotten in more traditional ways. I refer to In re Bergy and In re Chakrabarty. In each case, the issue was one of statutory interpretation. The Patent Office, in denying patentability, contended that Section 101 and its predecessors did not encompass living organisms. Elsewise, there would have been no need for separate enactment of the Plant Patent Act of

1930 subsequently codified in Title 35. Proponents of patenting, of which I am one, and ultimately the Court itself by a 3-2 majority disagreed. According to them, the legislative history was uninstructive, and passage of the Plant Patent Act could be readily explained by plant breeders' need for relief from the constraints of disclosure requirements uniformly applicable to utility patents. ~~I might add that~~ the same constraints of Section 112 are applicable to patents on microorganisms, though the disclosure problem in that connection is benefited by one's ability to incorporate in his disclosure organisms made available to the public ~~through one or another microorganism depository~~.

Bergy and Chakrabarty are now awaiting redecision by the CCPA in the wake of Parker v. Flook. Days following its decision of the latter case, the Supreme Court accepted cert in Bergy, reversed and remanded for reconsideration in light of Flook. The CCPA subsequently pulled Chakrabarty back for reconsideration in tandem with Bergy, and those cases have since been reargued.

What the Court will do in the wake of Flook is anyone's guess, considering the narrow majority by which the patentability issue was first decided. No matter what the outcome, I think it likely that the issue will find its way back to the Supreme Court.

One might ask what the decision of a computer patentability case, Parker v. Flook, has to do with the question whether living things can be patented. While the memorandum decision reversing Bergy sheds little light on this question, an answer may lie in some rather disturbing dicta in the Flook decision. There, Justice Stephens noted a dearth of Supreme Court precedent for software patentability doubtless owing to the recent vintage of the computer industry. He was conscious of the impact computer patenting would have in our society, and suggested that the Court should proceed cautiously in 'extending the patent system into areas of technology never contemplated by Congress.' Perhaps the same things could be said of patenting "life," and perhaps in reversing Bergy the Court was animated by reference in the Solicitor General's Petition for Cert to the "controversiality" of genetic engineering.

I suggest to you that all of that is utter nonsense and I commend to you my own article (naturally) at 60 JPOS 468 (1978) for a detailed exposition of the reasons why. Very briefly, it would be absurd to make controversy the judge of patentability. The patent system exists not to regulate new technology, but rather to foster its creation, and to bring it into public view. If the patentability of inventions were to be judged in inverse relation to their

ability to impact the way we live, then the Patent Office would surely become the domain of gadgeteers, while the very best of invention went unrewarded. And far from side-stepping a legislative role, I think that in passing the buck to Congress the Supreme Court has really assumed that role. That is, despite the broad language of the Patent Act, a forward looking statute which is written in contemplation of things not now known, the Court has said to Congress after each new field of technology is invented, you must retrospectively tell us whether it should be patented, and whether in fact it is the sort of thing that achieves the constitutional purpose of advancing science and the useful arts. I respectfully submit that to state that proposition is to refute it.

There are two views as to the importance or not of composition protection in this field, and each springs from the somewhat unique nature of the science involved. On the one hand, suppose I have a process for constructing a novel organism, and others practice that process to create the organism just before my patent issues. It is very likely that my process will never need be infringed, once the patent issues. Why? Because the organism can thereafter recreate itself, virtually a million-fold overnight.

It is far from inconceivable that the organism, through reproduction, can perpetuate itself throughout the seventeen-year term of the patent, without any necessary resort on the part of my competitor to reconstruction of the original progenitor. What has my invention availed me?

On the other hand, you will recall this little loop of DNA, or "plasmid" that I showed you earlier. every time our giant bacterial cell reproduces itself, it will also reproduce the plasmid. Why can't I get composition protection on the plasmid itself, and sue anyone I find using organisms that contain such a plasmid? Bear in mind that this little chunk of DNA, this "plasmid" is absolutely inanimate. One would think it as patentable as any other novel chemical substance. Quixotically, pending resolution of the right to patent life cases, the Patent Office has suspended examination of not only applications that claim living microorganisms, but also those that claim inanimate plasmids. You explain that, because I can't!

CONCLUSION

Now, this giant chromosome (indicating) has all the information on it you need to make an elephant. If it were really dictaphone tape, I doubt very much it would hold all the information, or misinformation I have subjected you to today. Before I make an elephant

or worse out of myself, let me conclude by suggesting two things to you.

To begin with, as a profession we are perhaps better insulated against "future shock" than others less used to dealing with innovation on a daily basis. We do more than simply make technology understandable to patent examiners, judges and jurors. Virtually on a daily basis, we assess the meaningfulness or not of technological advance and its relative importance to our society. Operating always withina framework of law, we are, or we should be, adept at weaving that technology into the fabric of our society. Accordingly, when issues involving science policy are nationally debated, it might be that we could make a contribution beyond merely preserving the incentives to innovation we view so essential. Our experiences, our combined legal and technical training, and our familiarity with innovation in a societal context ought to be made useful on a broader front. How we can do that as a profession, in any organized way, and the circumstances under which it would be appropriate for us to lend our aid, IS A SUBJECT WE SHOULD CONSIDER. ~~I leave to your imagination.~~ ~~I can not~~, e as one example, ~~the creation of~~ a ~~commission to study the ethical and other implications of genetic engineering research. What~~ contributions ~~could our~~

P.L. 95-622, 95th Cong, 2d. Sess. 1978.

~~profession make to such a study?~~ What ~~other~~ contributions can we make, that go beyond that mere defense of innovation, and make available to the public our special skills in understanding it, assessing and, sometimes, debunking it?

Secondly, with respect to genetic engineering itself, the new-found technology has been rightly compared, in its momentous nature, to the fission of the atom. It is probably more significant than that, and as significant in biology as man's first domestication of plants and animals. As physics brought us to the core of matter and energy, now molecular biology has stood us on the threshold of life itself. ~~A~~ Some modern-day Prometheus brought us the fire of physics, and ~~its~~ our recognition of its danger has not brooked its use. No more did early man return to the volcano, or to the sky, the fire that cooked his food. No more can we, or will we, return to our Creator the new power over life that we have won. To do so is simply not in our created nature. As when we reached for star-fire, as we now reach for life-fire, so in any great endeavor -- pray God guide our hand.

Thank you.

IN THE

Supreme Court of the United States

October Term, 1979
No. 79-136

SIDNEY A. DIAMOND, Commissioner of Patents and Trademarks,

Petitioner,

vs.

ANANDA M. CHAKRABARTY.

BRIEF ON BEHALF OF GENENTECH, INC., AMICUS CURIAE.

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"'Is it conceivalbe' I asked, 'that one day we shall create, in effect, biological machines—systems that can be used for productive purposes and will be composed not of plastic or metal parts, but of living organisms?' His answer was . . . unequivocal: 'We are already there. The great future of industry will come from biology.'"[1]

Interest of Amicus Curiae.

Genentech is a small venture capital corporation founded in California in 1976 to convert the promise of recombinant DNA technology into received benefits in areas as diverse as medicine, agriculture and energy. Research funded by Genentech at the City of Hope

[1]Toffler, *Future Shock*, 195 (Bantam ed., N.Y. 1970), reporting a conversation with Arne Tiselius, president of the Nobel Foundation.

National Medical Center in Duarte, California and elsewhere resulted in the creation, for the first time anywhere, of a bacterial organism capable of producing a human hormone. In subsequent testimony before Congress that achievement was hailed as a "scientific triumph of the first order" by Phillip Handler, president of the National Academy of Sciences, and as "astonishing" by Paul Berg, himself a pioneer in the field.[2]

More recently, Genentech and its City of Hope collaborators succeeded, with other genetically altered bacteria, in producing no less than human insulin itself. Press reaction included this, from the September 8, 1978 editorial pages of the *Los Angeles Times*:

> "The important and laudable achievement in insulin copying supports the positive expectations of scientists to the potential benefit of millions of persons now living and yet to be born."

And in July of 1979, in what *The Economist* hailed as a "remarkable feat"[3], Genentech married natural and synthetic DNA to create a microorganism capable of producing human growth hormone. The result will be unlimited availability of a substance heretofore in critical short supply for the treatment of dwarfism and, possibly, one useful for bone fracture and burn therapy as well.

Variously in collaboration with other private parties, educational institutions and, for that matter, agencies of the United States Government, Genentech is continuing research aimed at the beneficial application

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[2]*Hearings on Regulation of Recombinant DNA Research before the House Subcommittee on Science, Technology and Space,* 95th Congress 1st Sess. 27, 55 (1977).

[3]Issue of July 14, 1979 at 88.

of recombinant DNA technology in cancer treatment, in the creation of vaccines against a wide variety of viral diseases, and in other fields.

It should be clear that the issue before this Court transcends the narrow interests of the parties and that the Court's decision will have a profound impact on, for example, the question whether investments in research expenditures and recombinant DNA technology should be made in view of the character of patent protection available. In Genentech's case the patent incentive did, and doubtless elsewhere it will, prove to be an important if not indispensable factor in attracting private support for life-giving research. And where the Patent System facilitates the interposition of small but fruitful companies like Genentech in pharmaceutical and other industries traditionally dominated by major concerns, it operates to best purpose, as an essentially pro-competitive mechanism.

Having delivered very substantial benefits to the public in reliance on the patent incentive, Genentech is vitally interested in continued operation of the quid pro quo principle upon which the Patent System is based.

All parties have consented to the filing of this brief Amicus by letter, the originals of which are being filed concurrently with the clerk.

The Issues Presented.

The issues addressed by this amicus are:

Whether it is in the public interest to afford patents on newly manufactured microorganisms;

Whether, in the alternative, any public interest could be served by denying them; and

Whether it is appropriate for this Court, before Congress has acted, to essay the task of subtracting any particular technology from the compass of a patent statute plainly written to embrace technologies unknown to Congress at the time of passage.

In the view of this amicus, and particularly following the dismissal of *Diamond v. Bergy*, No. 79-136 as moot, the issue before the Court is decidedly not one of patenting either principles of nature or anything akin to them. Compare *Parker v. Flook*, 437 U.S. 584 (1978). The Chakrabarty microorganism, like those created by Genentech, is remarkable precisely because it is found nowhere in nature. Instead, at least in respect to what makes it useful, it was called into being solely by the hands of man.

Summary of Argument.

American experience has shown that the Patent System of the United States is one of the most ingenious engines for the inspiration of new technology ever conceived. In large part, the ingenuity of the system is attributable to two of its special characteristics.

First, the system seeks not to catalogue the past, but rather to compass the future. It perceives that the permissible subjects of patents are as broad as man's technological grasp, and so is written out in broad and forward-looking terms with the aim of extending our reach in every useful direction. Its purpose is not extended, but rather fulfilled, when a new-born technology comes within its purview.

Secondly, the Patent System is, out of necessity, neutral. It cannot be too finely tuned to the kind

(as distinguished from quality) of creation involved, if it is to achieve its task of encouraging the dissemination of what is new and imaginative and useful, so it can be finally judged in the marketplace of ideas and things. Most particularly must it abjure prior restraints, because they chill expression in literature and science alike. The neutrality of the Patent and Trademark Office requires that it leave to other agencies the regulation of technology, after the fact of its creation. Its different job is to inspire creations of every kind, and then before the fact of their creation.

Petitioner's argument from the controversiality of recombinant DNA technology is both misleading and irrelevant. It is misleading because the controversy has largely dissipated. It is irrelevant because controversiality cannot be made the judge of patentability, else the most revolutionary inventions would go unrewarded and the domain of patent law would be relegated to that of gadgeteers alone.

It is Petitioner, not Respondent, that would cast this Court in a legislative role. This Court is ill-equipped to determine when and then to what extent the needs of society require that any given technology be deleted from the broad compass of the patent laws. Congress, on the other hand, has that capability and has exercised it in the past, both prospectively and, as to already issued patents, retrospectively. See 42 U.S.C. 2181(a).

The new biology holds enormous promise in application for the public good. Much tangible benefit is already in hand. Despite the contrary view of Amicus The Peoples Business Commission, it *is* the job of the Patent System to generate greater momentum in such research and in all research that promises advan-

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tage. Regulating the product of research must fall to agencies other than the Patent and Trademark Office, which is itself inept as a regulatory tool. In any event, no regulatory purpose would be served by denying patents on microorganisms while continuing to grant them on processes of creating and using such organisms; while permitting academic research to go forward indifferent to either profit or patents; and while permitting even industrial practitioners to seek trade secret alternatives, so defeating the role of the Patent System as an information clearinghouse.

On the other hand, grant of microorganism patent protection is required to avoid opportunities for cynical evasion of patent laws as they attach to processes alone. Nothing in the legislative history prohibits such patents. Instead, the logic and greater purpose of the Patent System compels them.

Petitioner Is Seeking Judicial Legislation in Policy Areas Unsuited to Judicial Consideration, Proceeding From a Premise Wholly at Odds With the Logic of a Patent System.

No one will dispute the notion that patent laws are written to incent the creation of things outside the contemplation of those who enact such laws. Perforce, patent laws are written in large and prospective terms, so as to include "anything under the sun that is made by man".[4] The genius of the patent system is that it extends and enlarges useful technology. Having been designed to inspire new technology, the system is not itself "extended", but rather fulfilled, when the

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[4] *In re Chakrabarty*, 596 F.2d 952, 987 (1979), quoting both House and Senate reports accompanying the 1952 enactment of Title 35, U.S.C.

desired results are attained and new science comes under its protection.

The best science and the best of invention is that properly described as "revolutionary", a term that bespeaks profound and often sudden change in the way men live their lives. A common consequence of revolutionary invention is widespread impact at every level of society. Undue caution in admitting inventions of that character to the protection of patent would, in the end, fashion a result antithetical to that envisioned by Congress. Only the most mundane innovation would be rewarded, and the grant of patents confined to the very "gadgets" reviled by Justice Douglas, concurring in *Great A. & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 156 (1950).

Revolutions in science generate "empirical data" of the sort referred to by Justice Stevens, writing for the Court in *Parker v. Flook*, 437 U.S. 585, 595 (1978), in direct proportion to their impact on society. We agree that such data is grist for the Congressional mill, and ill-suited to assessment by the Supreme Court. For precisely that reason, we submit that if newly created technologies of wide-ranging impact are to be subtracted from the broad compass of patentability, it is Congress that in the first instance should essay that task. To paraphrase the brief of Petitioner.[5]

> "Congress, rather than the judiciary, is empowered and is best able to resolve the complex social, economic, and scientific questions frequently involved in such decisions, and, if [a deletion] is to be made, to tailor the statute to achieve precisely the desired ends."

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[5]Brief for the Petitioner at 9-10.

Congress has proven its ability to tailor the patent statute in exactly that fashion, as witness 42 U.S.C. 2181(a):

> "No patent shall hereafter be granted for any invention or discovery which is useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon. Any patent granted for any such invention or discovery is revoked, and just compensation shall be made therefor."

When that section was enacted atomic research was controversial in all its parts, and it remains so even to the present day. Yet Congress had the facility, as this Court does not, to limit its "tailoring" of the Patent System by the dictates of policy in a complex field, and it exercised it so as to proscribe only certain patents, while permitting such others as those later issued to Glenn Seaborg[6] for the creation of the isotopes that are Elements 95 and 96 of the Periodic Table.[7] The surgical precision of Congress' action in this regard stands in sharp contrast to the meat-ax approach Petitioner now urges. Thus, Petitioner would have the Court proscribe the grant of patents across the full length and breadth of a "vast"[8] field, one whose span includes everything from beer-making to gene-splicing, and then to do so because a *part* of that field is "controversial".

Endless mischief would result from adoption of Petitioner's approach to resolving "patent-ability" questions by reference to policies outside those embodied in

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[6]U.S. patents 3,156,523 and 3,161,462.

[7]Indeed, it was the Government itself which applied for and obtained those patents, Seaborg being its employee.

[8]Brief of the Petitioner at 20.

the Patent Act itself. Each time there arose a pioneer technology of societal consequence, courts would be asked to constrict the patent laws until Congress could adjust the competing policy considerations involved. The job of Congress would reduce to more or less piecemeal restoration of the Patent System, technology by technology. When each technology was restored by Congress to its rightful place within the broad and forward-looking language of 35 U.S.C. 101, only the efforts of those who created the technology would go unrewarded, for their patents would have in the meantime been denied. Petitioner's argument from caution in "extending" the patent incentive leads ineluctably to this absurd conclusion.

It is one thing to decry interstitial additions by the judiciary to the patent laws, as does the dissent below.[9] It is quite another to urge, as does Petitioner, interstitial deletion of whole technologies from the operation of those laws. The latter asks the Court to legislate in the stead of Congress, and then in areas peculiarly unsuited for judicial treatment. Most particularly should the Court eschew such action when Congress has demonstrated, as it did in enacting 42 U.S.C. 2181(a), its refined ability to both adjust the scope of the patent laws and to revoke patents whose interim grant appears to it, in retrospect, to have been improvident from the standpoint of policy.

The Argument From Controversiality Is Misleading.

Both Petitioner and Amicus, the Peoples Business Commission (PBC), refer repeatedly to the "controversial" aspects of genetic engineering, as if controversy

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[9] *In re Chakrabarty*, 596 F.2d 952, 1002 (Miller, J., dissenting).

were to be made the judge of patentability. The argument from controversy, we suggest, is both misleading and irrelevant. To begin with, animal cloning, test tube insemination and other extravagances have nothing to do with the minute concerns of Chakrabarty, and those in turn have nothing to do with gene-splicing, which alone has generated all the controversy. Even the concern over recombinant DNA technology has, we think, been greatly overblown in the briefs favoring reversal. Though hotly debated just a few years ago, DNA technology "is now in wide use" and, according to Dr. Walter Gilbert of Harvard University, "worries about the dangers of genetic engineering have all but disappeared".[10] In fact, the Director of the National Institutes of Health has approved the large-scale production of insulin by recombinant DNA organisms.[11] In fact, at last count the same Government agency was itself funding fully 717 research projects in the field, to the tune of some 91.5 millions; preliminary studies conducted by the Government have reportedly failed to demonstrate any significant danger associated with recombinant DNA research.[12] Against a backdrop of active promotion of such research by European governments and concern over possible loss of this country's technological lead in the area, a spokesman for Congress' Office of Technology Assessment has suggested

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[10]As quoted in " 'Glamour Stock' Could Help Cancer Patients", *Los Angeles Times,* issue of January 21, 1980, Part I, pp. 3, 16.

[11]Letter dated December 13, 1979, Elizabeth Milewski, Scientist Administrator, Office of Recombinant DNA Activities to Dennis Kleid, Chairman, Biosafety Committee, Genentech, Inc.

[12]"Where Genetic Engineering Will Change Industry", *Business Week*, October 22, 1979, 160, 164.

that "government's stance may change from regulation to promotion" of the science.[13] And while Petitioner suggests[14] that it was "continuing controversy" that led the National Institutes of Health to revise its guidelines for research in the area, it was actually the *diminution* of that controversy which led the agency to significantly *relax* those very guidelines.[15]

The Argument From Antagonism to Science.

The attempt to cast this Court in a legislative role is nowhere more evident than in the brief amicus of the Peoples Business Commission (PBC), whose essentially Luddite philosophy[16] would have the Court stand the Patent System on its head, denying patents so as to avoid

> ". . . generating a greater momentum in research and development of genetic engineering technologies . . . [which] . . . in turn, will lead to the rapid proliferation of genetic techniques in the areas of energy, agriculture, medicine, industrial processes and many other aspects of the nation's economic life."[17]

But the question before the Court is neither one of ethics, nor philosophy, nor politics. It is one of statutory interpretation, of grammar leavened with reason. Despite the invitation of PBC, it is not for this Court

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[13]*Id.*, quoting Zsolt Harsanyi.

[14]Brief for the Petitioner at 19.

[15]Op. cit. supra, n.12.

[16]The Luddites of early nineteenth century England sought to prevent the spread of labor-saving machinery by the simple expedient of destroying it. For industrial purposes, bacteria that produce human insulin can be regarded as life-saving machinery.

[17]Brief Amicus Curiae of Peoples Business Commission at 3.

to question Congress' wisdom in enacting either the Plant Patent Act[18] or the broader provisions of 35 U.S.C. 101, nor to attempt, like King Canute, to command the tide of technological development.

It is true that genetic engineering is pregnant with potential for altering the human condition. As advances in electronics and plastics led to the implantation of pacemakers and artificial heart valves, so advances in genetics could one day lead, by gene transplants, to the elimination of sickle cell anemia, Tay-Sachs and other genetic diseases. But to suggest, as PBC does, that affirmance of the decision below would bind the Court to construe the Act as permitting patents on all forms of life, even "a human being manufactured to desired specifications"[19] extends literalism beyond reason. One might as well argue that the definition of "meat food products" in 7 U.S.C. 182(3) extends to anthropophagy because it can be literally construed as inclusive of human parts, or that because humans are members of the kingdom Animalia, the Secretary of Agriculture is empowered under the Animal Welfare Act of 1970 "to protect the owners of [humans], from the theft of their [humans]," [20] so resurrecting the fugitive slave laws. The patentability of homunculi[21] is not the issue before the Court, and altruism is misplaced if, on behalf of invisible bacteria that can be freeze-dried to a powder having no semblance of livingness, it argues for the dissuasion of life-giving research.

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[18]Plant Patent Act of 1930, 35 U.S.C. 161 et seq.

[19]Op. cit. supra, n.17, at 25.

[20]See 7 U.S.C. 2131, 2132(g).

[21]Manikins made in flasks by alchemists.

PBC asserts "the public's right to a diversified gene pool composed of naturally occurring life forms"[22]. It wants noting that the naturally occurring life forms most likely to be impacted by the flowering of recombinant DNA technology are those no one will miss at all, deadly vectors associated with such horrific diseases as Lassa Fever, the scourge of Southern Africa; Influenza, which in 1918 slew more than died in the Great War; Epstein-Barr virus, which potentiates one form of cancer in blacks, another in Orientals, and causes mononucleosis in Caucasians; rabies; shingles; foot and mouth disease; and endless others. Even cancers could fall across a broad front, if the promise of interferon produced by recombinant microorganisms holds true.[23]

At bottom, it is clearly in the public's interest to retain patent incentives for inventions in the life sciences in general, and in recombinant DNA technology in particular. If controls are to be imposed on research in those areas, judicial abandonment of the patent reward is not the way to do it. Congress has proven,

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[22]Brief Amicus Curiae of Peoples Business Commission at 13. The accompanying argument that patenting microorganisms could diminish the 'diversity of the gene pool' on planet earth can scarcely be credited, when any shovel-full of backyard sod can yield micro-organic life in endless variety, and when genetic engineering itself permits the creation of new varieties, so tending toward greater and more useful diversity.

[23]Interferon is produced in the body to stimulate defense mechanisms against cancers and viruses. Small amounts have been conventionally produced in the laboratory at enormous expense, but recombinant DNA technology may yield a cheap and plentiful source of the material. Just weeks after the filing of Petitioner's brief, a precursor form of interferon was reportedly made in that way by altered bacteria. "Scientists Produce Protein in Laboratory," *The Los Angeles Times*, edition of January 17, 1980, Part I, p.28. The achievement was reported by Biogen, S.A. which, like Amicus, is a small venture capital company.

time and again, its ability to devise more suitable means of control, as witness a host of regulatory agencies. The more so should such questions be left to future Congresses where the record so far in hand is overflowing with evidence of the beneficial practice of recombinant DNA technology, yet contains not a single instance of any associated harm.

The Denial of Patents on Microorganisms Would Accomplish No Regulatory Purpose.

It can readily be demonstrated that the denial of patents on microorganisms would serve no public interest at all, let alone those for which Petitioner and PBC contend in particular.

To begin with, denial would not diminish the administrative burden of patent examination one iota. Whether the patent claim is directed to an oil-degrading microorganism itself or, say, to a method of combating oil spills that involves deploying a mixture of organism and straw on a spill, the same issues of novelty, utility and unobviousness must be resolved, and in either case the organism must be described and distinguished from the things that have gone before.

Again, it is idle to speculate that denial of patents on microorganisms would be an effective means of curbing their construction, when everyone agrees that patents can continue to issue on methods of constructing them or, more commonly, methods of using them in industry.

Where the limitations of process patents did discourage patent filings, work at an industrial level would, perchance, go forward anyway. As one commercial practitioner has suggested, "you keep your proprietary

strains under lock and key"[24]; that is, forever a trade secret. Were this to happen, the only result would be defeat of one principal purpose of the Patent System —to enhance learning through encouraging disclosure of useful information.

And if the diminution of meaningful patent protection did act as a disincentive to industrial exploitation, no corresponding diminution in biohazard, if indeed any exists, would result. That is so because the controversy over hazard has nothing to do with patents. A biohazardous experiment involving bacteria would be as dangerous if practiced at a laboratory bench in academe as when done at large in industry—perhaps more so, through inattention to the economic consequences of carelessness. Academic and industrial hazard in this area, if it exists at all, is at least in parity. A single virulent organism escaping a University laboratory could rival, virtually overnight, a million-fold escape from a factory. The point is that the denial of patents could inhibit only industrial application of the new science, perhaps the most useful kind. Academicians could continue equally "hazardous" experimentation, indifferent to either profit or patents.

Finally, there is the alternative of patents on plasmids themselves. Plasmids in recombinant bacteria are like carburetors in engines. Properly installed, they permit the bacterial engine to cough into useful life, producing the precious substances whose genetic information they encode. But plasmids are absolutely inanimate. Each building block of the plasmid (and plasmids can be built) is an absolutely dead bench chemical. All of

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[24]"Where Genetic Engineering Will Change Industry", *Business Week*, October 22, 1979, 160, 172 (quoting Leslie Glick, of Genex).

the building blocks in the aggregate are little else. The chemical composition of the plasmid they form is absolutely definable. By every imaginable test, the new plasmids that confer near-miraculous properties on everyday organisms ought to be patentable, just like any other man-made chemical of value. And just as someone who makes, uses or sells an automobile containing a patented carburetor can be sued, so too one who makes, uses or sells a bacterium containing a patented plasmid should be be subject to suit for infringement.

Two things remain to be said about plasmids.

First, pending the resolution of the *Chakrabarty* matter, the Patent and Trademark Office has suspended the examination of patent applications that claim plasmids[25], despite the universal practice in this country of granting patents on inanimate chemical substances and despite the fact that no claim to a plasmid is before this Court. Even an adverse opinion of the Court with regard to the patentability of living things, then, should be careful to preserve the patentability of new but dead chemicals, like plasmids, that meet all the normal criteria of patentability. It is interesting to observe that in the Chakrabarty application the Patent and Trademark Office proved quite willing to grant claims directed to the combination of living organisms and straw, presumably for use in combating oil spills. Can it be said that Congress intended patents on living organisms inside inanimate bits of straw but prohibited them in the case of inanimate bits of chemical inside microorganisms, or are we beginning to draw distinctions that border on the silly?

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[25]Private Communication, Examiner A. E. Tannenholtz to the Author, November 13, 1978.

Secondly, the continuing availability of patents on plasmids undercuts the proposal by PBC that this Court's decision be aimed at disincenting the practice of genetic engineering. If plasmids are patentable *in se,* and the Patent and Trademark Office has failed to articulate any reason why they are not, then the practitioners of recombinant DNA technology will be largely unaffected by a ban of patents on microorganisms.[26] Ironically, only those in more conventional fermentation industries will suffer because in those, new microorganisms are gotten in other ways, without the creation of new and independently patentable plasmids.

At bottom, the Patent System is an ingenious vehicle for the inspiration of new technologies. It is an inept tool for their regulation and the attempt to surround it with a regulatory aura, because illogical, is deserving of rejection.

Microorganism Protection Is Required if Cynical Evasion of the Patent Laws Is to Be Avoided.

The fear has been widely expressed that the United States increasingly is losing its technological lead, and that the loss of that lead can be expected to severely

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[26]The plasmid question, we add, offers the Court an interesting opportunity to accommodate the interests of both parties in the present matter. *Nothing* in the legislative history of the Patent Act could be construed as proscribing patents on dead chemicals like plasmids. The grant of patents on plasmids could satisfy the needs of a burgeoning and bountiful industry, without reaching the issue of patents on life forms of any kind, let alone higher forms. And although no "plasmid" question is before the Court, the predisposition of the Patent and Trademark Office referred to in the text (which is tied by it directly to the outcome of the present matter) should command both the attention of this Court and care in phrasing its opinion.

impact America's balance of payments and other indicia of economic health. And yet, increasingly, that picture is brightening. According to one commentator:

> "[I]n newer industries the level of research is high and American innovation is the envy of the world."[27]

And, of course, one of the new industries to which the author points is genetic engineering itself. In another article,[28] encouragingly entitled "U.S. Innovation: It's Better Than You Think," the authors find increasing evidence that new enterprises, most particularly in "the exciting science of genetic engineering", are behind a resurgence of domestic innovation. The encouragement of domestic innovation is important, and that can best be done by a strengthened patent system, as both Congress and the President have agreed.[29] In the important field of genetic engineering, that system would be best strengthened or, for that matter, restored by the grant of patents on microorganisms.

Virtually every one of the most remarkable feats of recombinant DNA technology has involved the creation of a new microorganism. But once a single microorganism has been created, in the culmination of what may have been years of work, the process of creation may need never be repeated because, once made,

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[27]"Innovation—Has America Lost Its Edge", *Newsweek,* June 4, 1979, 58, 59.

[28]*Dun's Review*, March, 1979, at 55.

[29]125 Cong. Rec. H22, 912 (daily ed. Feb. 27, 1979); 430 BNA Patent, Trademark & Copyright Journal (BNA); 125 Cong. Rec. 567, 6715 (daily ed. May 24, 1979); Industrial Innovation Coordinating Committee Subcommittee on Patent and Information Policy, Draft Report on Patent Policy §2 (III) (1978); 430 Patent, Trademark & Copyright Journal (BNA) A-2.

the microbe does all the work. It reproduces itself and its new capabilities, time and again. The process can go on indefinitely, certainly throughout the seventeen year term of a patent that may in the meantime have issued.

Absent patent protection on the microorganism itself or, at the least, on its key components,[30] numerous opportunities will arise under which others:

> ". . . would then be allowed to reap the fruits of the American economy—technology, labor, materials, etc.—but would not be subject to the responsibilities of the American patent laws."[31]

After disclosure of the invention whose practice creates the organism, but before actual grant of the patent, others could practice the invention *once,* making an organism that would thereafter perpetuate itself without infringing the later-issued patent. Again, even after the process patent had issued, another could repeat the process outside our borders and beyond the reach of the patent. The resulting organism and its progeny could then be freely introduced to the United States, leaving the process patent holder to his remedy, uncertain at best, in proceedings before the International Trade Commission.[32] Indeed, in the special circumstances of microbiological patenting, it could become possible for the cynical "infringer" to make no organism at all, but rather to obtain and use the inventor's own microorganism from a culture collection in which it has been deposited to satisfy the disclosure require-

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[30]See text accompanying note 26, supra.

[31]*Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 534 (Blackmun, J., in dissent, quoting the opinion of the Fifth Circuit in the same matter, 443 F.2d 936, 939).

[32]See 19 U.S.C. 1337, 1337a.

ments of the Patent Act.[33] Here the holder of a patent confined only to the process by which his micro-organism was created must, absent affirmance of the decision below, sit idly by while another uses that very organism to compete with him in producing an end-product that is itself unpatentable because earlier available from other sources. That is so because the law at present prohibits any restriction on third-party use of deposited organisms, once the patent has issued, and instead then leaves the creator of the organism to his infringement remedy.[34] Absent claims on the organism itself and in the circumstances described, that remedy may be nonexistent.

The iniquitous evasion of the patent laws that could result can be avoided by confirming in inventors their right to effective patent protection on the products of their often-stupendous labors, even when those products are "alive". And to do so requires no extra-territorial extension of the patent laws, as was sought in *Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518 (1972), but rather only that their purposes be effectively implemented *within* our borders.

The Argument From Legislative History.

It should come as no surprise to Petitioner that the decision below is the first holding of its kind in almost 190 years of American patent jurisprudence.[35] The question has simply never before come before any court, and under Article III of the Constitution the courts are bound, case-by-case, to resolve only

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[33]*In re Argoudelis*, 434 F.2d 1390 (CCPA 1970).

[34]*Feldman v. Aunstrup*, 517 F.2d 1351 (CCPA 1975).

[35]But see Brief for the Petitioner at 13.

the controversies that parties put before them. Petitioner has accordingly been obliged to mine not any body of judicial precedent, but rather a narrow and, in the view of this Amicus, vanishing vein of legislative history.

We believe that the pertinent legislative history (or, in the present case, essential non-history) of the Patent Act reduces to a small number of common-sense propositions apparent from the brief of Respondent and those of other amici:

First, there is no meaningful evidence suggesting that in enacting 35 U.S.C. 101 and its predecessors Congress thought anything about the patentability of microorganisms, either yea or nay. Instead, it clearly sought by broad language to encompass every *new* and useful process and tangible thing that could meet the criteria, including description criteria, of the general patent laws.

Secondly, Congress enacted the Plant Patent Act[36] to broaden the availability of patents, so as to satisfy plant developers otherwise unable to protect their creations because of product of nature and descriptional difficulties arising under the general patent laws.

Thirdly, the exclusion of bacteria from the Plant Variety Protection Act[37] was, pretty clearly, no more than Congressional codification of the decision in *In re Arzberger,* 112 F.2d 834 (CCPA 1940), holding that bacteria were not "plants". That exclusion says nothing contrary to patentability of microorganisms under the general patent laws, in the event they could

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[36]Plant Patent Act of 1930, 35 U.S.C. 161 et seq.

[37]Plant Variety Protection Act of 1970, Pub. L. No. 91-577, 84 Stat. 1542, 7 U.S.C. 2321 *et seq.*

conform to utility, novelty, non-obviousness and the more rigid description requirements of those laws.

Suppose that when some Congress had before it the job of enacting or amending the patent laws this testimony had come before it:

> "There exists, out in the future, a new science whose application could result in giant strides toward the elimination of disease, and of hunger, and the creation of whole new energy sources. It can be discovered and applied to those ends if the patent laws you enact are broadly drawn so as to encompass, and to incent, acts of invention that will bring the new science into view."

Would there later be any doubt that by the broad language Congress *did* use in 35 U.S.C. 101 it intended to incent the attainment of those very goals? Would there be any doubt that it intended to encompass the new science, even though its workings remained unknown when the law was drawn? And is there any doubt but that Congresses of the past *did* have salutary goals like those in mind every time the patent laws came under their hand?

We urge that the Patent Act be construed so as to sustain its large objectives, the ones clearly intended by Congress. To do so will confirm the patentability of microorganisms and both encourage a beneficent science and ensure that broad and forward-looking incentives remain for those who would pull the next technology, the one now invisible because still down over the horizon of the future, into view and into use.

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Conclusion.

For the foregoing reasons, the judgment of the United States Court of Customs and Patent Appeals should be affirmed.

January, 1980.

Respectfully submitted,

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March 21, 1984

Dear Tom:

It gives me pleasure to present you with a replica of the Entrepreneurial Company of the Year medallion awarded to Genentech by the Stanford Graduate School of Business last year. In your role as Vice President Corporate Affairs and as a member of the Management Committee, you have been a key ingredient in our success and our subsequent recognition by institutions such as Stanford. I appreciate your contribution to our record and reputation and am pleased to give you this medallion as a symbol of our achievements.

Bob

Officers of Genentech Meet the Place Pigalle, mid-1980s
Left to right: J. Gower, R. Swanson, D. Martin, K. Raab, T. Kiley, W. Higgins, L. Lavigne, R. Ring and M. Ross

A TALE OF TWO TRIALS[1]

THOMAS D. KILEY

THE INNS OF COURT SOCIETY, SAN FRANCISCO, CA

MAY 24 , 1990

Introduction

Here is a tale of two trials on the same subject, one to a judge in England, the other to a jury in America. The results were different. So was almost everything else. I'm tempted by my experience in the two matters to paraphrase Oscar Wilde: 'America and Britain are two peoples divided by a common system of Justice'.

One trial took place in Wilmington, the other in London: two cities with a lot in common. It is remarkable to note that every letter in the word "London" can be found in "Wilmington" except a "D", and that one is right up front in "Delaware." Wilmington started off with du Pont's black powder factory on Brandywine Creek just after the American Revolution. But there is nothing to support the idea that Guy Fawkes had any connection to du Pont. Same idea, different revolution.

In London we were in the catacombs of the Royal Courts of Justice, a great pile dating from the reign of Victoria. The U.S. matter was tried on the top floor of the J. Caleb Boggs Federal Building, erected in the reign of Richard Nixon. The upper gallery in the London Court was sealed off against IRA bombers. In Delaware, there were metal detectors against 'IRAb' gunmen and other gunslingers not members of the bar. The judges in both places wore black dresses. It is a small world.

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[1] © 1990 Thomas D. Kiley; formerly Vice-president and General Counsel and Vice-president for Corporate Development, Genentech, Inc.

t-PA

The subject of these lawsuits was an invention that's only important when a clot stops the flow of blood to your heart. Depending on whether part or all of your heart dies, what happens next is that part or all of you dies!

The body makes in small quantities a molecule called t-PA that dissolves clots gradually, as wounds heal. The molecule is large and complicated, four hundred times more so than aspirin. Nature makes it by hooking together 527 amino acids like beads on a string. But in the body, Nature doesn't make enough, fast enough, to stop a heart attack.

The Genentech invention had to do with t-PA got by genetic engineering in large enough quantities to find and dissolve heart clots in a hurry. Think of it as a combination of a smart bomb and Pac-man.

Parties

The parties in the litigation included Genentech, the first genetic engineering company in the world. Genentech used genetic technology to make available copious quantities of human insulin, human growth hormone, and interferon. And in 1986 it first patented (in Britain) gene-splicing methods by which t-PA can be made in amounts sufficient for widespread medical use. Genentech's work followed that of its partner, the ancient University of Leuven in Belgium. Dr. Desire´ Collen of Leuven had been the first to isolate from natural sources t-PA of pharmaceutical purity.

The Genetics Institute or "GI" was the East Coast, the Harvard University, answer to Genentech. Starting late, it raced with Genentech to be first to make t-PA using gene-splicing. It got beat flat out, late by a year. GI's effort was bankrolled by Baxter Travenol, a major health care company. Travenol sold out to Wellcome after Genentech's patent rights came into view. Wellcome is a multi-billion dollar pharmaceutical company, now publicly traded, that travels under cover of a so-called "charitable trust". It is more familiar to San Franciscans as the company that brought us the AIDS drug AZT for anyone with $10,000 a year to pay for it.

Overview

On the day Genentech's British patent issued, Genentech was sued by Wellcome in the Patents Court of London's High Court of Justice. Wellcome sought to break the patent because it wanted to make and sell t-PA itself, though it had played no role in the pioneering research that brought the drug forward.

Wellcome would succeed in breaking Genentech's British patent. A U.S. patent then issued, and on that day Genentech sued Wellcome and GI in Delaware. Leuven University weighed in later with a patent on t-PA itself. Before long, an American jury found that all patents were valid and had been infringed, both by Wellcome and by GI's so-called "second generation t-PA". And within a few weeks Wellcome announced that as a result of the U.S. verdict it was dropping *worldwide* development of both first and second generation t-PA.

So at the end of the day, and though Wellcome won the first round, Genentech won the scalp!

Patent Law

Predictably, in the U.S. litigation Genentech's opponents accused it of unfair competition and antitrust violation for having presumed to seek enforcement of the patents. In the event, those counterclaims were rejected. But the main business of the two trials had to do with patent law. What is that all about?

Government encourages competition in innovation by giving patents for the best of it. It also encourages competition by denying patents on second-rate inventions, new wrinkles that aren't hard for ordinary people to come up with. In return for patents, inventors tell the public how to make the invention so that can be done freely when the patent expires.

Patent fights in the courts commonly center around three things: was the invention ordinary, or not; and did the inventor tell the public enough, or not; and does the defendant violate or "infringe" the patent claims, or not.

Of these, the most difficult is the question whether the invention rises above the ordinary to the point of deserving a patent.

Justice Frankfurter called it the most metaphysical question in the law. In our British trial there were quibbles about the adequacy of the information given in the patent, but most of the *evidence* had to do with this more metaphysical question: whether what Genentech did would have been *obvious* to ordinary workers in genetic engineering. Did it rise to the level of "patentability"?

In the case of t-PA, that question would engage the attention of witnesses from the National Academy of Arts and Sciences, from The Royal Society of Britain, and from among winners of the Nobel prize itself.

To deal with the question, we need to know more about the race to "clone" t-PA or more accurately the race to find the DNA the body uses to make that substance. If the DNA could be found, it could be put into cells that would act like microbial factories, churning out t-PA in amounts able to save lives.

Just how hard was it to isolate that DNA from among all those in the body?

The Race For t-PA begins

The story begins in the late 1970's when workers looking for agents to dissolve blood clots were obtaining from the arteries of cadavers, and from uterine tissue gotten by hysterectomy, crude extracts of a previously unknown but active substance that would later be called "t-PA". Desire´ Collen discovered that t-PA was produced in large quantity by melanoma cancer cells named for a patient, Bowes, from whom they had been obtained. After great labor, Collen had purified enough t-PA to treat a patient suffering from a blood clot in the kidney. In reporting the work Collen recognized the unsuitability of Bowes cells for large scale production and called for efforts to make t-PA by gene-splicing. Before long, he was sending samples of the Bowes cells to scientists around the world for use in their own investigations.

James D. Watson was no ordinary man, having shared with Francis Crick the Nobel Prize for elucidating the famous double helix structure of DNA. His remarkable book about that effort, The Double

Helix, reveals him as a fierce scientific competitor.[2] The laboratory Watson directed at Cold Spring Harbor, New York was world famous as a center for research in molecular biology.

In July 1980 Jim Watson established an effort at Cold Spring Harbor to find in the Bowes cell the DNA for t-PA. Operating under Watson's direction the Laboratory's Associate Director, Joe Sambrook, would spearhead the project. Sambrook was a member of Britain's Royal Society, in the company of such as Isaac Newton, Charles Darwin, and Stephen Hawking. With Tom Maniatis, a founder of GI, he would later author the first compendium of laboratory techniques for cloning. Today, that book is referred to as the "cloning bible." Sambrook was no ordinary man.

A company was formed and its efforts funded by Baxter Travenol, who would have patent rights. The company was to be managed by Angus McIntyre, whose diary and other records of the Cold Spring Harbor efforts would illuminate in later litigation whether it was "easy" to clone t-PA.

In February 1982, 19 months after the Cold Spring Harbor effort began, Mr. McIntyre would record: "Joe Sambrook -- ready to give up!" This was despite an earlier letter reporting a rumor that Genentech *had* succeeded in getting a clone. In that letter, Mr. McIntyre had said:

> "Joe Sambrook had originally felt the project was at or beyond the limits of present knowledge. If Genentech has a clone, it establishes the project as do-able . . . ."

Urging Baxter's continued support, McIntyre went on to say: "After Kitty Hawk, people didn't stop designing airplanes." Baxter did continue funding, but the further efforts of the Watson group proved futile. Unassisted, they simply couldn't make the project fly.

The Genentech Effort

Genentech started three months after the Watson group, in collaboration with Collen. Genentech had got an exclusive license

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[2] J.D. Watson, The Double Helix, W. W. Norton & Co. Critical Edition, G. S. Stent, ed., N.Y. (1980).

under the Leuven patent applications on t-PA itself and supplies of the material for study, looking for a hook to fish out the right DNA from all the wrong DNA in the cells. Genentech calculated the t-PA needle was buried in a haystack of about 10,000 'wrong' DNAs.

The task would prove arduous. Dianne Pennica, a key Genentech worker, put together nearly a year's worth of 12 hour work days, back-to-back, weekends included. She worked under the direction of Dave Goeddel. BusinessWeek has called him, only somewhat sacrilegiously, the "master cloner of the Universe". He had led the teams that cloned human insulin, human growth hormone, the interferons, and many other Genentech "firsts". In an international meeting in July 1982 Dianne revealed, to a standing ovation, Genentech's success in cloning t-PA. A commentator called the announcement an "historic event."

Other Efforts

Others had found the task no less easy. At the British trial, Wellcome brought forward two young men from Umeaa University, near the Arctic Circle in Sweden. Before Genentech announced, and before quitting, they had succeeded in finding about 15 percent of the DNA. One of these workers, who had failed using methods different from what actually worked, said the right method would be "obvious". The other, who actually used that method, said nothing about obviousness. Under cross-examination he said of his own work, "It almost killed me". An ordinary man?

If all this was so hard, how did Wellcome get its clone? Well, when Jim Watson's group proved unequal to the task, it turned the project over to GI. GI claimed, improbably, to have cracked open the t-PA safe one day before Genentech published its combination. At trial we showed the GI effort involved a host of *avant garde* devices, reagents, and techniques that were unavailable to ordinary men, things referred to in internal documents with encomiums like "liquid gold" and "magic bullet machine".

Nevertheless, Wellcome would bring forward the GI success and the partial success of the young men from Umeaa as evidence of the "obviousness" of what Genentech had done.

That proposition was curiously at odds with GI's preparation of a patent application on its own "independent" clone. The application

was never filed. A memorandum by a Baxter Travenol attorney named Flynn usefully recorded advice he had given:

> 'Since Genentech seems well ahead GI must be careful about filing any basic patent application, lest it be faced later with explaining to a District Court judge why an earlier Genentech patent on the very same subject matter should be considered invalid.'

The memorandum was made available to us by the gods of legal discovery, who act in inscrutable ways. Mr. Flynn was spared embarrassment by his untimely death. Wellcome would not be. The memorandum came into evidence over its fierce objection, giving new meaning to the old saw, "in like Flynn."

Now there is the background for the supposed "obviousness' of Genentech's achievement. One supposed that was what the British trial would be all about, since Wellcome conceded that its product, which differed from Genentech's only by a single bead on the chain of 527, infringed the patent.

Let's go now to London and introduce the *dramatis personae*, some of whom wore wigs that look like the scalp I'm holding today.

The British Trial

A. Lawyers with Wigs; Lawyers Without Wigs

In the Royal Catacombs of Justice we found Jack Whitford, a longtime Patents judge known colloquially as "Jumping Jack" because he was nimble at getting to the right answer. So quick was Jack, it was said, he could often settle his mind without waiting to hear both sides! Our matter was to be his last major trial before retirement.

At trial, Justice Whitford lived up to Hollywood's conception of a proper English judge. His impromptus were well-planned and delivered with great cheer from his seat "halfway up the wall".

I'm told Justice Whitford had apple cheeks and twinkling eyes; but from my seat deep in the well I could see only the top of his wig. It was not the cocker spaniel variety I expected; but rather more a crew cut or sheared-off version. His punch lines were good enough to

make me happy I was out of sight. I spent a lot of time biting my pencil, snuffling in the well until I could catch my breath. Less fortunate were the barristers behind and above me, within sight of his Lordship's guns. When he told them they hadn't got their garters on, or were otherwise undressed, they were stuck with replies like "Much obliged, Milord." Same, same, there and here. We say "Thank you, your Honor."

We were ably represented by Stephen Gratwick, a Queen's Counsel sometimes referred to as "Stevie Wonder" for his courtroom accomplishments. He could get three syllables out of the letter "P." Gratwick has *Presence* in the courtroom. He is the Norman sort of Englishman. Neither his nose nor stature would have been out of place in the Court of the first William. Gratwick is the best cross-examiner I have seen, bar none. He could have got answers out of Adam quicker than God did in the Garden of Eden.

Stephen Gratwick's single fault was dismissing too frequently what I thought should be said, based on no more than experience, seniority, and understanding of the peculiar system in which he has lived all his professional life. "Jury points," he would say, "not appropriate here!" It made me crazy.

Gratwick was instructed by Simon Cooke, an elfish wizard whose great-greats founded his firm a century and a half ago. Simon must be a Saxon. Tenacity, common sense and plain talk come naturally to him. When not leading his firm he keeps under hand cultivation a half acre of vegetables and feeds migratory birds in three ponds dug out of the Essex countryside. His "Da" was the oldest night-fighter in the air Battle of Britain. Simon, like Stephen, is good people.

Now to the other side. There was first Robin Jacob, Q.C., also known as "Bobbin' Robin". His style was that of a bright but nervous schoolboy, hopping anxiously from foot to foot before his headmaster. He hadn't time to deal with all this evidence stuff; but there must be something wrong with an over-reaching patent, one that would "stifle research"; one granted just because Genentech happened to get "first to the post" at the end of a hard-fought race. I found his arguments distasteful. I must say the courts of England had a great appetite for them. The scalp in my hand is not his. He did all his client asked of him, and thinned *my* hair in the process.

Robin Jacob was also served by solicitors. Smarmy in correspondence and bearded in prospect, they hovered around the proceedings like a cloud of gnats. They would flit away when Mr. Jacob asked petulantly where the evidence could be found. But they would come back to sip our blood when Jumping Jack had got it running out on the table.

B. Expert Witnesses

Now, there were expert witnesses there in London, mainly to help understand what was and was not obvious to mere mortals.

Expert witnesses are to patent litigation what on-lookers are to an accident scene. Everyone expects them.

First to appear was a Wellcome expert, a silky-tongued professor of seamless testimony who would bridle when American counsel referred to his university as "Lie-cester". In the event, the professor proved the "leaster" of the experts in England and America.

Genentech fielded a Nobel laureate, members of America's National Academy of Arts and Sciences, and a member of the Royal Society. In truth, there were two, since both the Nobel Laureate and the Fellow of the Royal Society were also members of the National Academy.

George Stark pulled the laboring oar among the Genentech experts after I recruited him using Rudyard Kipling's method: "Softly, softly, catchee monkey."

George is an American who holds a high seat in Britain's Imperial Cancer Research Fund with laboratories just across Lincoln's Inn Field from Simon Cooke's offices. "George," I said, "could you walk across the way every now and then, and see Mr. Cooke? Have tea and a cookie.[3] Maybe tell him a little about molecular biology."

Next, "George, would you mind designing a simple experiment to show how big the haystack was? Not to worry, we'll do the work at Genentech."

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[3] A biscuit.

Then, "George, we've collected all the papers written on cloning since the time of Adam and Eve. There are only 300 of them. Won't you just sit down and read them? Take the whole weekend if you have to."

Why does anyone put up with this? Well, it was George's fate that he should do so. Right before the London trial he was elected to the National Academy. We sure know how to pick 'em. Just before the U.S. trial he was elected to the Royal Society. I've about got George persuaded if he stands up one more time for Genentech he'll get the Nobel prize. I'm working on it.

Meantime, George needs to work on his arithmetic. In London he was suprised to learn not everyone knows that three is halfway between one-third and nine! By the time we got him to the jury in Delaware he understood that whatever scientists may do, jurors do not think in logarithmic terms. *Moral -- Practice makes perfect.* [4] George was perfect in Delaware.

Our Nobel prize winner was Paul Berg, honored for gene-splicing work on the same day in 1980 that Genentech went public. Just before the British trial opened I heard Robin Jacob say to Stephen Gratwick, "*Owehh*, will you call Berg?" Gratwick replied in kind, "*Owehh.* If one has an Exocet, it would be a shame not to use it".

Herb Boyer was the scientific founder of Genentech. After Genentech's initial public offering, he shared with the Ayatollah Khomeni honors as runner-up for Time magazine's Man of the Year. They were both edged out by Ronald Reagan.

In getting the Nobel prize, it was Paul Berg who edged out Herb. Framed on my office wall at Genentech was a page from the San Francisco Examiner. The headline read: "Genentech Jolts Wall Street." Under it was Paul's picture, for having got the prize. Under Paul's nose I taped a moustache, so Herb wouldn't recognize Paul when he came into my office! Well, Herb has to recognize him now, for saying in both British and American proceedings that t-PA represented success in the most difficult cloning project ever.

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[4] Compare any "Moral" in Theobald Mathew, Forensic Fables by Q, Butterworths, London (1961). These portrayals of the foibles of people who wear horsehair to work seem quite accurate.

We got to Paul in a roundabout way. After Watson and Crick did the double helix, Sydney Brenner worked with Crick to solve the genetic code, describing how the information in genes gets translated into action. Sydney is a Fellow of the Royal Society and a Companion of Honor to the Queen. I had tried to recruit Sydney as an expert witness but his boss, the head of Britain's Medical Research Council, refused permission. Said Mr. Sir James Gowan: "Sydney, if Wellcome loses, there will be a vast political ramification. I am adamant you shall not do it". Sydney, obliged to remain neutral, had put me on to Paul.

Because of Sydney's neutrality, I was pleased later to see his name put forward by Wellcome to become expert advisor to the Court of Appeals. "Ohhh-kay", I said, obligingly. Sydney did sit with the Court, but Genentech had little profit from it. In thanking Sydney, the Court said he:

> "...played no part in the judicial decision-making process, nor has his advice had any influence on that process other than to provide a scientific factual background. "

In fact, Sydney did good service. The Appellate Court more or less got the science right. Now, if only they had appointed an expert in common sense!

James Watson, whose group had failed at t-PA, would say in American deposition testimony that what Genentech did was "pedestrian science." For understandable reasons, his testimony was never offered here or in Britain to show what Genentech had done was obvious. The last time I saw Jim Watson we were pacing the subterranean halls of Justice in London, during a break in the trial there. "It's like a tennis match," he marveled; "It's like a movie." It was a *silent* movie so far as he was concerned.

Jim's failure to rebut the British testimony of his fellow Nobel Laureate was important to later proceedings in the U.S. Patent Office. The old admission by silence trick. And I believe his failure to get to t-PA before Genentech, despite a head start of several months, weighed heavily on the jury here. Absent experts! I love 'em the best!

C. Obviousness

The evidentiary phase of the British trial focused on whether cloning t-PA had been "obvious" in law. Genentech's answer to the metaphysical question had three legs. We would show the task was surpassingly hard, even for the "master cloner(s) of the Universe". We would show that others, including those led by a Nobel laureate, had failed. And George Stark, having analyzed the whole literature of cloning, would show by a half-dozen criteria that finding the right DNA in the Bowes cell was the most difficult cloning exercise since Eve was got from Adam's rib.

We sought to prove t-PA was in the very highest percentile of difficulty, so far above the median that to clone it was beyond the skill of average or "ordinary" scientists.

Wellcome replied that others had more or less succeeded, more or less at the time of Genentech's work, *give or take a year!* If the literature was used to compute what skill was ordinary, it should be examined more or less at the time of Genentech's success, *give or take a year!* The Umeaa workers had quit only because Genentech beat them to the post. Otherwise they could have finished handily. The failure of the Watson group was a mere failure of administration. Cold Spring Harbor was an ivory tower operation that simply hadn't got its act together. As for Genentech's own perspiration, 'Well,' said Wellcome, 'where's the *inspiration*? Everyone knew that t-PA would be nice to have!'

D. The Result

I had thought the purpose of the patent system was to encourage people to 'get their act together'. I left London on Independence Day 1988 knowing we had won. Mr. Bobbin' Robin Jacob confided he thought he had gone down. Five days later the news came at 4:00 am, the midnight of the soul. We had lost!

Justice Whitford, in a barely comprehensible opinion, had held the patent was too broad! In British press accounts that followed our patent would be called "greedy and over-reaching" because it was not limited to t-PA "bead" sequences identical to what we had isolated. To claim in a patent as Genentech had done would "stifle

research" and thwart the public interest being pursued by such institutions as the Wellcome charitable trust.[5]

The opinion was so opaque that press releases from the parties differed on whether the invention had been held *not* obvious, as the later appellate decision said it had. Justice Whitford did say the Genentech workers, though representing more than "an average degree of skill," could not get to the result without "a very great deal of painstaking experiment".

There had been no pleaded defense of "too broad", and little evidence about it. Wellcome's own admission of infringement had distracted attention from the subject. When it came up in argument we showed the defense "too broad" had been eliminated in Britain's new Patents Act. The Court of Appeals would later agree.

When you are ambushed at trial with a new defense, my experience says one of two things will happen. One happened in America, when new defenses came in at the eleventh hour and were dumped by the Court because they had not been forecast in the pleadings. The other thing happened in Britain, beginning with avuncular assurance to the effect that 'We are all big boys, a great deal of money and the attention of astute counsel has been expended, and we are confident no harm will come from entertaining the new defense.' *Then the harm comes.* The idea seems to be the rules of pleading and fair notice are only applicable in unimportant matters. But for matters of importance, "Brittannia waives the rules."

Within weeks of the early morning phone call, I had resigned from Genentech; I will say for unrelated reasons. But before my resignation could become effective, and despite the British result, I would need to get a United States patent on t-PA. The effort would take nearly half a year.

Genentech's U.S. Patent

In their dealings with the Patent Office American attorneys must fulfill a duty of utmost candor. They may neither misstate

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[5] The single amino acid difference in the Wellcome molecule (one of 527 "beads" on the string) was an experimental artifact, a mistake that conferred no apparent advantage. Because Wellcome had admitted infringement, the Court had no occasion to learn the Wellcome and Genentech products were virtually identical.

anything important; nor omit what needs to be said if the Patent Examiner is to make an informed decision whether to grant a patent.

My job became to put before the Patent Office everything that had been said in Britain against our right to patent, and the British Court's opinion against our patent, and then persuade the Patent Office that Britain had been wrong. I did that.

The Patent Examiner here got to see every exhibit from Britain, all the testimony, and Justice Whitford's opinion. She got every cloning paper from Adam's rib until t-PA and a road map to guide her through everything we submitted.

While this process was underway, the FDA approved Genentech's t-PA. The Food and Drug Commissioner hailed the product as "a dramatic example of the benefits of biotechnology [that would] usher in a new era of pharmaceutical development."

After the FDA got it right, the Patent Office used our road map to get its part right. Genentech got its patent. Soon afterward, the Genentech workers were honored in a Capitol Hill ceremony as "Inventors of the Year." Genentech's t-PA went on to set industry records for best first year sales of any pharmaceutical.

The U. S. Litigation Begins

Where I grew up, whenever a new family moved into the neighborhood the local merchants would welcome them, driving up in a station wagon filled with free merchandise. It was called a "Welcome Wagon". When Wellcome moved in on t-PA, I made up a shirt for the Genentech law team. On it, a ferocious "Lawdog" is bounding forward, his jaws agape. Far behind his dripping teeth, the stub of a tail is wagging. The legend reads, "Wellcome Waggin'."

One good turn deserves another. On the day the U.S. patent issued, the Genentech lawdogs sued in Delaware Wellcome and all its stalking horses: the Wellcome trust, Burroughs Wellcome (its American subsidiary), GI, a Wellcome-GI joint venture called "WelGen", the whole bunch.

The ancient University of Leuven came in as plaintiff with its own patent on t-PA itself, and by its sympathetic presence offset the "charitable' entity in which Wellcome was cloaked.

We had had enough of judges, and asked for a jury. We accused of infringement not only Wellcome's product, but also GI's so-called "second generation" product. We said that because Genentech was a pioneer it was entitled to broad protection, broad enough to cover Wellcome's variation and anything else that was "equivalent" to our molecule.

This time, Wellcome relied on its single amino acid difference. I calculated the Wellcome product was better than "99 and 4/100ths percent pure" t-PA, but Wellcome denied infringement. GI said its own second generation product was remarkably different, and also avoided the patent. I thought they had tried to make enough changes to fool the Court, while keeping enough identity to fool the blood clot. Maybe the clot would think it was t-PA, even if the Court didn't. And maybe the jury would agree with the clot. As pioneers, we believed we were entitled to broad protection against knock-offs, despite what Britain had said about our "grasping" and "overbroad" patent.[6]

The British Appeal

While American discovery proceeded, we were heard again in Britain, up at the Court of Appeals. Our matter was the first to come there under Britain's 1977 Patents Act. We were a test case. How pleasant.

Lord Justice Purchas led the Court. He is a plummy, roast beef sort of fellow. In any role on Masterpiece Theater, he would be called "Colonel" or "Guv'nor".

Next in seniority came Dillon, L.J. Spare, brooding, vulturine, he hung over the bench as if impatient, waiting for something to die.

Finally, there was Lord Justice Mustill, a past speaker here. Mustill combined felicity in language with a certain felinity in attitude. Through argument he seemed to be licking his lips at the

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[6] In America, the argument is that the accused product is "equivalent" to the claimed invention and in equity ought to be considered an infringement. Unhappily for GI, internal documents said its product and t-PA were "equivalent". Ahhh, the gods of discovery work in mysterious ways, their wonders to perform!

prospect of dining on the novelties our matter raised. I was concerned, rightly in the event, that mind games appealed more to him than the morality play to which we invited his attention.

These gentlemen all agreed we were wrong, but with nothing Justice Whitford had said, and each with little the others said. The whole exercise reminded me of the grim novella by H.P. Lovecraft, At the Mountains of Madness.[7]

All agreed no "too broad" defense could be found in the Act. Purchas then held the patent was too broad because it *might* cover improvements that *might* be patented in their own right. Mustill agreed, Dillon was silent. American law has permitted dominant patents of that kind for more than a century.

Mustill acknowledged the importance to order and justice of proper pleading but said "otherwise healthy formalities would be out of place" in our matter. Now, really!

Purchas thought Genentech's work met the standard for patenting. Mustill and Dillion disagreed.

Dillon thought ability had nothing to do with 'patent-ability'. Purchas disagreed. American law is flat contrary. Genentech's own achievement Mustill put down to "administration," the lack of which evidently excused Watson's failure.

Purchas found patentability in Genentech's having isolated and deciphered Nature's elusive code for t-PA. Mustill thought invention had to lie in what was done *once given* that DNA, itself a 'natural principle' whose discovery could not justify a patent. American law is contrary. Dillon said he "would not accept many of Mustill L.J.'s conclusions" but didn't have to because it was obvious to *attempt* what Genentech had done. American courts uniformly reject "obvious to try" as the standard.

Our patentability statute was rewritten in 1952 to center on extraordinary skill and to exorcise "flash of genius" as the test for

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[7] H.P. Lovecraft, In At the Mountains of Madness, Arkham House Publishers, Inc., Sauk City, WI (1964)

"invention". Nearly forty years later, Justice Mustill was looking in England for an "inventive spark", a "spark of imagination." Finding none, he must rule against Genentech despite his "admiration" for "an excellent piece of work" in "the most difficult [project] to have been tackled at the time."

Mustill's focus on the mental aspect of invention troubled other members. Longstanding precedent denied to the hypothetical ordinary man any inventive cast of mind. Mustill thought anyone must have "some substantial measure of ingenuity," just to operate in the DNA field. Therefore, the legal test for patentable invention must be whether one has exceeded what Mustill called "the permitted maximum of inventive thinking," whatever that is supposed to mean.

Go figure! It's too mental for me, all 316 pages of it! In the wake of this gobbledygook British lawyers will spend the next century trying to figure out what, anything, is now patentable in that Kingdom.[8]

I do know we lost. It was as if Justice Whitford had punished us for talking out of turn. Then a unanimous appellate court upheld our freedom to speak. Then one Lord Justice knocked our teeth out, the next one sewed our lips together, and the last said we couldn't chew gum!

And there the British patent was left. Dead as a doornail. Dead as a patient who doesn't get t-PA when he needs it. Dead as the next patient who doesn't get a life-saving drug when there's no incentive to spend millions on the hard work of inventing it.

According to Justice Mustill, "In the end, obviousness is a jury question." Hear that, Mr. Gratwick? Are you listening? Let's go back to that good old American jury.

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[8] Because the issues under the new Act were ones of first impression, British jurisprudence might have benefited from a further appeal to the House of Lords, almost certain to have been entertained. From Genentech's standpoint, however, a helter-skelter decision of the Appellate Court was preferable to a potentially cogent, unanimous but unfavorable decision of the highest Court, from the standpoint of impact on parallel litigation here. And it might have been asking too much of the Lords to reverse back-to-back decisions favoring a revered British institution against an upstart company of Americans.

The American Trial

A. *Dramatis Personae*

Our Delaware jury was made up of firemen, carpenters, and other solid citizens. All had high school diplomas, one three years of college. In the event, it went a long way. No molecular biologists, no protein chemists, no cell biologists. The usual story.

Judge Joseph Farnham maintained a low profile before the jury. His deadpan demeanor well concealed that he was dazzled by the brillance of our case. This was a comforting view because the alternative, that he was baffled by the whole business, was too terrible to contemplate.

Raised eyebrows were Judge Farnham's best feature. Without cluttering the appellate record with messy rulings on objections, they often signalled questions should be rephrased. Local counsel maintained a robot labeled "Judge Farnham," before which I assume young lawyers were encouraged to practice declamation.

The witnesses in America were the usual suspects, rounded up from the British trial and returned to the stage here.

Dimitri Dennis Allegretti stood up as counsel for Genentech. He says his first name is Russian, his second Irish, and his third Italian -- except when he is stopped by an Irish traffic cop. The officer says: "What's your name?" "All-e-gretti," he says. "O.K., O'Grady, I'll let you go this time." Allegretti is from the Windy City, Chicago, the city of big shoulders. He is tough.[9] He has heart.

GI's attorneys took the high road of "No infringement, your honor" and left the dirty business to Wellcome's counsel. To see in your mind's eye *that* fine gentleman, imagine yourself on the stand, as I was. Nightline's Ted Koppel points his treacly finger right in your face. "When did you stop committing patent fraud?" he says.

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[9] For example, both defendants asked the jury for attorney fees as an element of damages
on the counterclaims, to punish our temerity for having haled them into court. In reply, Allegretti called them "a bunch of whining crybabies."

B. The Treacly Finger of Fraud

Too often in America, patent infringers claim to be defending the patent system by exposing patents gotten by fraud. Samuel Johnson said: "Patriotism is the last refuge of a scoundrel." Rather than push hard its British argument of obviousness, or focus on its claim of non-infringement, Wellcome chose to wrap itself in the flag. My flag.

I was accused in my dealings with the Patent Office of having "deep-sixed" adverse evidence. Other harmful information was said to have been "buried" in what I sent to the Patent Examiner, beyond hope of her finding it out. The roadmap I provided was treated as obscurantist and laced with misstatement.

A second Genentech patent in suit had been obtained by another attorney hired by me, an absent witness. Wellcome referred to him, time and again, as "Mr. Kiley's former law partner" as if this were proof enough of venality.

The same attorney had obtained Dr. Collen's own patent. In winning a number of prestigious awards bestowed by his peers in science, Collen had beat to t-PA a certain gentleman from Vienna who now took the stand. He had read through the history of Collen's dealings with the Patent Office and found what he called "150 misrepresentations," several of which he was actually willing to identify!

To sew together this shroud of supposed fraud, Wellcome brought forward a certain professor of patent law. Though not registered to practice before the Patent Office, he was pleased to accept $400 an hour to point the finger in this, his twenty-second outing as a witness expert in patents. But despite all that experience he floundered when asked at my request to name names. Who had lied? Who had concealed? Dr. Collen, who selflessly supplied the Bowes cell line to the world? Petite Dr. Pennica? Dr. Goeddel? Any other inventor? Dr. Berg, in his affidavit? Dr. Stark?

When my name was finally put to him, he grasped it like a drowning man reaching for a lifeline. 'Mr. Kiley did! Him and his former law partner!' I guess the idea was any juror will hang a

lawyer, as the professor would, if he could just get his hands around a rope.

The best evidence of my own *bona fides* was the effort I had made to put before the Patent Office all that had been said against us in the British proceeding. So much for lies and concealment. But under rulings of the Court that had been requested by *Genentech* counsel, the submission *couldn't be mentioned* lest the jury be exposed to the British result! Nothing I said could move counsel to open up that issue. Sometimes it is hard to sit in the courtroom, trusting in counsel, trusting the jury to see through to the right answer. Ask any client.

C. The Jury Speaks

After a month of evidence, argument and instruction, the jury retired. It deliberated for about ninety minutes, more if it didn't stop for lunch. Then its verdict came in.

There was no patent fraud, no unfair competition, no antitrust violation by Genentech. All patents were valid. All products of all defendants infringed all patents.

Conclusion

The jury's practical grip on the real world of work, risk and reward had returned everything taken away by the mental manipulations of a brain-bound judiciary in Britain. I had come home to "jury points," things common people understand. Not Uncommon Law,[10] but "Common Sense" in the sense of Thomas Paine.

Like Paine and Guy Fawkes were, I still am. Still a revolutionary. Sometimes I think Mr. Fawkes put his black powder under the wrong building!

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[10] A. P. Herbert, Uncommon Law - Being 66 Misleading Cases, Methuen London Ltd. (1969). More foibles of fellows in wigs. No fables.

Kiley Bungee Jumping into Nanaimo River Gorge, Vancouver Island, 1994

KIRITIMATI MIRACLE

In the language of the central Pacific nation of Kiribas, "ti" is said "ess"; thus Kiritimati or "Christmas" Island, found without human habitation on that day by Captain James Cooke while en route to his destiny, killed in the surf of The Sandwich Islands.

The morning that marks the Savior's borning
I saw a mirage of rainbows glow
beyond the thin, vegetal fringe
and sunward in the great atoll.

Only the susurrus of wind in clothing
spoke of my coming, wading to marvel,
and the crunch of branching coral breaking
and plash and purl of the water round.

Trevalley salvoing down the lagoon,
chased milkfish over the flat's edge flying;
hazed them up in flight head high,
from shallow water beneath my thighs.

The refracting veils of mist falling
from their frantic airborne show
announced in spectral colors how
sun became on the holy day.

Silhouettes of frigate birds
arrowed in waters as fish fled out,
like all confused concerning
what feast day place was proper.

Sun back-lit black-tipped reef sharks,
small just enough to belly on the flat
but arrogant still in lazy patrols,
insinuated to cruise for cripples.

Here and there the errant yellow blowfish
puffed up with indignation swam;
while skates waved pandemonium aside
with black and undulating wings.

Among it all bonefish ghosted;
their nervous quartering ways
spoke in volumes of indecision
whether to partake or fly the feast.

All coursed about as if I not there,
making mayhem at my feet,
and me in wonder gaping
as if witness to world's morning.

I grinned so wide my lips cracked,
and I wept rainbows.

P-BRANE

All the p-branes could be found as solutions of the equations of supergravity theories in 10 or 11 dimensions.

Stephen Hawking

Augustine said our minds
No more can logic God
Than a hole in the sand
Can hold the mighty sea.

But I've been talking
With Stephen Hawking,
Who claims a P-Brane
Could be a membrane

On which are written
In *p* dimensions
All the declensions
Of God's creation.

It's hard for me to figure,
But I know it's likely so--
His brane is bigger, better trained,
Holds unfettered holey water,

Better far than my pea-brain.

INDEX--Thomas D. Kiley

Sally Smith Hughes

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