UNIVERSITY OF CALIFORNIA, SAN DIEGO

BIOTECH'S PERFECT CLIMATE: THE HYBRITECH STORY

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Sociology (Science Studies)

by

Mark Peter Jones

Committee in charge:

Professor Steven Epstein, Chair
Professor Gerald Doppelt
Professor Andrew Lakoff
Professor Michael Schudson
Professor Steven Shapin

2005

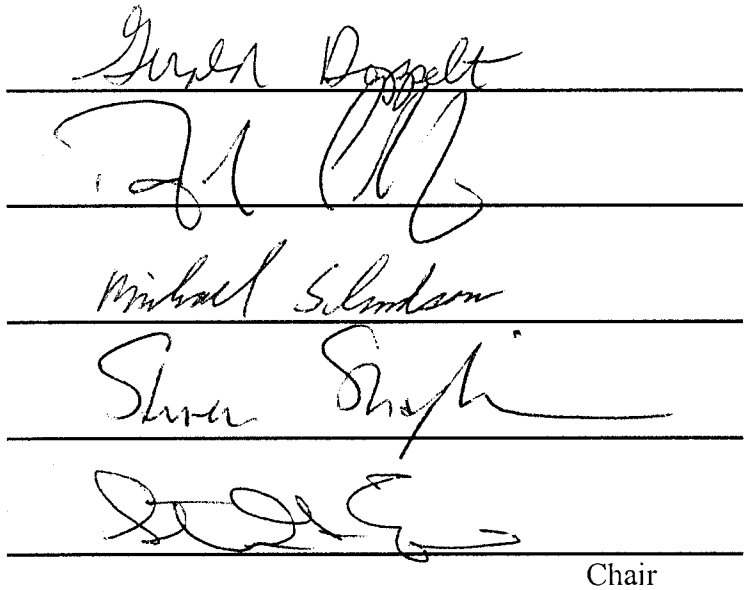
INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

ProQuest Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

The dissertation of Mark Peter Jones is approved, and it is acceptable in quality and form for publication on microfilm:



Chair

University of California, San Diego

2005

For Anth, as big as the world.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

Many people helped me with this project, but I want to give special thanks to Steven Epstein and Steven Shapin. Their influence was enormous. Abi Barrow and the late Bill Otterson provided access to San Diego's biotech entrepreneurs. This work would not have been possible without their assistance. The research was supported by a grant from Ewing Marion Kauffman Foundation.

MARK PETER JONES

VITA

1992	B.A., Sociology, Indiana University at South Bend
1993-1995	Teaching Assistant, Department of Sociology, University of California, San Diego
1994	M.A., Sociology (Science Studies), University of California, San Diego
1997-1999	Associate Lecturer, Department of Sociology, University of California, San Diego
2000-2005	Visiting Lecturer, Department of Sociology, Indiana University at South Bend
2005	Ph.D., Sociology (Science Studies), University of California, San Diego

ABSTRACT OF THE DISSERTATION

BIOTECH'S PERFECT CLIMATE: THE HYBRITECH STORY

by

Mark Peter Jones

Doctor of Philosophy in Sociology (Science Studies)

University of California, San Diego, 2005

Professor Steven Epstein, Chair

This work is a sociological history of the origins of the biotechnology industry in San Diego, California. It focuses on the professional biographies of scientists and executives at Hybritech, Inc., San Diego's first 'biotech' company. Hybritech was founded in 1978. After the company was acquired by the large pharmaceutical corporation, Eli Lilly, people affiliated with Hybritech went on to found over fifty additional biotech firms in the city. The Hybritech story illustrates the centrality of social networks in the formation and execution of entrepreneurial projects, and in processes of technological and organizational innovation. Specifically, it shows how academic scientists, venture capitalists, and managers from the pharmaceutical industry worked together to create a new social space for conducting scientific work. This space was characterized by a 'hybrid culture' that mixed practices from academic laboratories and industrial R&D operations and encouraged entrepreneurial venturing. It has been sustained over time through the continuing formation of new biotech start-ups in the city. The analysis was based on extensive interviews with financiers, executives, and scientists belonging to San Diego's life science community.

I. INTRODUCTION

A recent Forbes magazine piece on commercial biotechnology identified San Diego, California as a leading site of activity and progress in the field.[1] The article recounted the story of Steve Dowdy, a forty-three year old assistant professor of medicine at the University of California, San Diego:

> In January last year he gave a lecture at the UCSD Cancer Center on 'in vivo protein transduction,' a means to deliver biologically active molecules, such as therapeutic peptides and proteins, inside the cell. Two senior professors, both of whom had turned their research into biotech companies, approached Dowdy afterward and told him he should start a company. Four days later he met with San Diego venture capitalists introduced by his colleagues. By the end of March the company, Ansata Therapeutics, had raised $5 million from Avalon Ventures and Domain Associates for a 50% stake.

Delivering large macromolecules reliably to cells inside living bodies is a very difficult thing to do. If Dowdy's technology works, it could solve a lot of problems for a lot of people. It could become a very valuable tool to possess. But if Dowdy had made such a discovery twenty-five years ago, he would not have been encouraged to commercialize the research, and he would not have been connected almost instantly to local sources of capital and managerial expertise ready in waiting to assist scientific entrepreneurs. Twenty-five years ago, risk capital and entrepreneurial know-how were relatively scarce in San Diego. Bioscientists were not regularly patenting and commercializing their inventions. They were not becoming involved in

[1] Kerry A. Dolan, "Best Places: San DNAgo," Forbes, May 26, 2003. The scientific journal Nature has also recognized San Diego's prominence in biotechnology. A recent supplement includes a number of brief articles on the past, present, and future of the city's life science community and its biotech industry. See "San Diego," Nature Outlook December 11, 2003, 426: 689-721.

entrepreneurial ventures. But stories like Dowdy's have become commonplace in San Diego. What happened?

BIOTECH BEACH™

San Diego, California is today a productive and widely recognized center of biomedical science. It has been since the 1960s, when several world-class institutions of scientific research, including the Scripps Research Institute, the Salk Institute of Biological Studies, and the University of California, San Diego, were built in close proximity to each other, on high bluffs overlooking the Pacific Ocean, a few miles to the north of the city's port and urban districts. Each of these institutions commenced operations by recruiting prominent life scientists from around the globe. Attracted by promises of first-rate scientific resources and professional opportunities, and by the region's Mediterranean climate, as well, the new arrivals came expecting to advance the boundaries of knowledge in the life sciences, expand and refine the technical capacities of modern medicine, and earn the most prestigious prizes offered to investigators in these fields. Many have done just this, and they, their projects, and their reputations, have, in turn, persuaded many more collaborators, colleagues, and students to conduct scientific work on San Diego's sunny palisades.

For bioresearchers, San Diego today represents the 'big time.' It conjures up images of sandy beaches and clear blues skies along with challenging scientific work; swimsuit models, perhaps, along with molecular models and prestigious letterheads. It's not hard to imagine ambitious young life scientists daydreaming of San Diego as they suffer through dreary winters in distant, chilly climes. Steve Dowdy, who moved from Washington University in Saint Louis to UCSD in 2001, says of the city: "I'll

never go anywhere else. It's scientific paradise, as far as I'm concerned."[2] Steve Engle, CEO of La Jolla Pharmaceuticals, a San Diego company that works with antibody technologies invented originally at the University of California, understands the imagery and the appeal. He likes to invite potential recruits to his firm to visit the city. When they come, Engle escorts them around town, taking advantage of the climate and natural beauty of the place to entice them. "When they live in Chicago or Scandinavia," he says, "it's a great opportunity for them to get the heck out of Dodge. I take people from the East Coast over to the Pacifica Café, and they stare past my shoulder at the ocean while I stare at them."[3]

San Diego has always had magnificent scenery. Now that it has science in abundance, too, what destination could be more attractive for talented biologists wishing to 'have it all,' to mix stimulating work, professional success and recognition, and leisure or adventure in an idyllic geographic setting?[4] For bioresearchers, San Diego is now one of the few places in the world 'where the action is.' Kary Mullis, one of several Nobel laureates in physiology or medicine with ties to the city, sums up its allure in this way: "...at least with biological scientists, they come here to be

---

[2] Dolan, "Best Places: San DNAgo."

[3] Cary Groner, "California Dreamin,'" Biopeople 38, April 1, 2002. Joseph D. Panetta, President and CEO of BIOCOM/San Diego, the region's leading life science trade association, relates personal conversations with two of the city's scientific luminaries: "I asked Jonas Salk why he came here and he said the weather. I asked Francis Crick why he came here and he said the weather." See Paul Smaglik, "San Diego: California Dreaming," NatureJobs March 13, 2003, 422: 240 – 241.

[4] According to psychologists' instruments that purport to measure satisfaction, Californians are no more satisfied, or 'happier' than people living elsewhere (although many apparently assume that they must be). See David A. Schkade and Daniel Kahneman, "Does Living in California Make People Happy? A Focusing Illusion in Judgments of Life Satisfaction," Psychological Science 9, 1998: 340-346. Moving to Southern California may not consistently deliver anticipated psychic benefits, but scientists who relocate to San Diego could be an exceptional group.

around other biological scientists. That, and the surfing."[5] The life sciences are alive and well in Southern California. San Diego's now famous academic institutions were founded on the idea of bringing high profile, cutting-edge biological and medical research to the city, and they succeeded.

For a brief time in the 1960s and 1970s, these institutions stood alone on their perches high above the beaches and rocky coves of the Southern California shoreline. In the past twenty-five years, however, the mesas and canyons surrounding these cathedrals of science and higher learning have become heavily populated by new biotechnology companies and sleek industrial parks constructed to house them.[6] These locales now serve as geographic centers of gravity for thousands of people and billions of dollars of venture and corporate capital. On the northern fringes of the city, much dusty coastal scrub has been replaced by ribbons of concrete, imported palm trees, and state-of-the-art pharmaceutical laboratories obscured from view by shiny modern and postmodern facades. The city of San Diego has established a presence, a tentative foothold, in the ethical drug industry. The pharmaceutical trade has long been dominated by large international corporations headquartered 'back east' in the

---

[5] Scott LaFee, "A Salute to San Diego's Nobelists: Gala at Hotel del Coronado Timed to Echo Stockholm Event," San Diego Union Tribune December 11, 1999.

[6] The term 'biotechnology' is somewhat vague. If read broadly as 'the uses of life for human purposes,' then the ancient arts of baking, brewing, agriculture, and animal husbandry can be included under this rubric. See Robert Bud, The Uses of Life: A History of Biotechnology, Cambridge: Cambridge University Press, 1993. In common usage, 'biotechnology' refers to recombinant DNA techniques, the tools of molecular biology and molecular genetics, but also many belonging to biochemistry, cell biology, microbiology, immunology, and other biological specialties. These methods are often applied in combination with techniques derived from organic chemistry, various fields of engineering, and a host of other disciplines not ordinarily classed as life sciences. In addition to health care, the chemical industry and modern agribusiness are other fields that have been impacted significantly by biotechnologies. Applications in these areas share many technical and, to a lesser degree, certain organizational family resemblances with those in biomedicine, but naturally there are also significant discontinuities as well. This study is concerned exclusively with the health care industry.

United States, and in Europe and Japan. These giants still rule the world of drug design and manufacturing, but small biotechnology companies presently constitute a new locus of innovation in the field, and San Diego owns a substantial piece of the action.[7] The city features the third largest concentration of commercial biotechnology firms in the world.[8]

Although sensitive to the mercurial fortunes of the industry as a whole in larger national and international contexts, the biotechnology community in San Diego

---

[7] When referring to biotechnology as a sector of the health care industry, I mean to indicate companies of recent vintage (i.e., started within the past thirty years) that generally share the following characteristics: they pursue research and development programs with scientific techniques invented in academic laboratories, not in corporate pharmaceutical houses (although this is rapidly changing as research conducted in commercial settings yields new biological tools); they are in the business of using these techniques to design therapeutics, diagnostics, and drug delivery systems, or to compile genomic or bioinformatic databases; their R&D, clinical testing, and manufacturing activities are regulated and monitored by sections of the FDA; they are typically financed in their initial stages by venture capital; and, when they manage to go public, they usually issue stock to be traded on the NASDAQ exchange. This categorization corresponds to that employed by financial analysts and the business press; it classifies firms by rough historical, financial, organizational, and technical criteria within the health care industry. Apart from this broad usage, the term 'biotech' carries little meaning to practitioners in the field. They certainly recognize interests and problems common to firms with similar financial and organizational histories, but they naturally make much finer technical distinctions. They locate companies in industry niches defined by very specific markets, and, within them, product development strategies and narrow areas of technical specialization.

[8] Numerous studies have corroborated this ranking. See Joseph Cortright and Haike Mayer, Signs of Life: The Growth of Biotechnology Centers in the U.S., Washington, D.C.: Brookings Institution Center on Urban and Metropolitan Policy, 2002. The two leading regions, according to most reports, are the San Francisco Bay Area (where biotech firms are scattered among various South and East Bay suburbs) and New England (with most companies clustered around the Boston-Cambridge area). However, as Southern California industry folk are quick to point out, San Diego's concentration is the densest. If the number of biotech ventures situated within the confines of a single municipality is taken as the measure, then San Diego, with over two hundred, is far and away the world leader. Industry booster Joseph D. Pannetta, president and CEO of BIOCOM/San Diego, says, "San Diego now lays claim to the most concentrated and diverse life science cluster in the world. More than 35,000 people work at...400 companies located within the county's 4,200 square miles. That's 38 percent more life science companies per square mile than the Bay Area, a region long thought to be the center of biotech." See Joseph D. Pannetta, "The State of San Diego's Biotechnology Industry," San Diego Daily Transcript, September 18, 2002. (Included among Pannetta's "400 companies" are numerous manufacturers of medical devices, scientific instruments, chemical products, and other medical and scientific goods and services; the number of dedicated biotech firms in San Diego county at the time was 216). Density is not merely a matter of bragging rights. Significant economic advantages may accrue to interdependent high-tech firms conducting business in close proximity to each other within a

continues to expand – at a rate equaling that of any other region. Each year, millions of dollars in venture capital are dedicated to new life science companies in various stages of development, and dozens of R&D partnerships are forged between local firms and large corporations in the health care industry.[9] As is the case with other centers of commercial 'biotech' activity, San Diego features a reasonably favorable business environment and a critical mass of localized bioscientific expertise. And now, more than twenty-five years after the first biotechnology start-up appeared in the city, there exists a well-established institutional infrastructure that provides requisite human, material, technical, and financial resources to high-tech ventures.[10] The eventual prospects of commercial biotechnology are very much uncertain and dependent on the future performances of firms and research teams as they engage the difficult task of bringing competitive diagnostic and pharmaceutical products to health care markets. Still, the nascent industry in San Diego perhaps has the potential to become a long-term staple of the local economy.[11]

---

single, integrated policy regime. See AnnaLee Saxenian, Regional Advantage: Culture and Competition in Silicon Valley and Route 128, Cambridge, MA: Harvard University Press, 1994.

[9] In 2000, venture fund investors poured a record $402 million into new San Diego life science companies. See San Diego Regional Economic Development Corporation, San Diego Book of Facts, San Diego, CA: San Diego Regional Economic Development Corporation, 2002.

[10] See Ross DeVol, Perry Wong, Junghoon Ki, Armen Bedroussian, and Rob Koepp, America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions, Santa Monica, CA: Milken Institute, 2004. This study asserts that San Diego's biotech industry is the most 'sustainable' in the nation, because of the research infrastructure (bioscientists, academic research institutions, and research funding) that supports it, and its demonstrated vitality in the past and present (in terms of new firm, job, product, and wealth creation). Following San Diego are Boston and North Carolina's Research Triangle. San Diego boosters will surely be citing this report for some time to come, since it enables them to proclaim that 'We're #1.'

[11] Edward J. Blakely, Kelvin W. Willoughby, and Nancy Nishikawa, "The Economic Development Potential of California's Biotechnology Industry," California Policy Seminar Brief 3, 4, 1991.

Many in the community are wagering that, in the 21st century, the continued emergence and growth of small biotechnology companies in San Diego will (along with similar developments in telecommunications, microelectronics, and software)[12] enable the city to keep pace and remain competitive in the emerging post-industrial global economy. Civic leaders in business, government, and the academy have become enthusiastic boosters. They look to high-tech industries like biotechnology to deliver jobs, expand the municipal tax base, attract skilled workers, and contribute in many ancillary ways to the social and cultural vitality of the city.[13] They are working cooperatively to accommodate and encourage high-tech development, to create an institutional environment and a policy regime that will perhaps spur the formation of

---

[12] Mario C. Aguilera, "S.D. Hotbed for New High-Techs / Survey Ranks Area Tops for Jobs in Southern California," San Diego Daily Transcript, March 23, 1995. A recent analysis conducted by the Progessive Policy Institute, a Democratic Party-sponsored think tank, ranks San Diego fifth among large U.S. metropolitan areas successfully adapting to the "new economy" and positioning themselves for future economic prosperity within it. See Robert D. Atkinson and Paul D. Gottlieb, The Metropolitan New Economy Index, Washington, D.C.: Progressive Policy Institute, Technology and New Economy Project, April 2001. The indicators used to analyze metro 'high-tech' performance include the export orientation of manufacturing; the number of "gazelle" companies (those with sales growth of 20% or more for four straight years); rates of new company start-ups and IPOs (initial public offerings); the concentration of professional and technical "knowledge" workers; the number of science and engineering graduates from local colleges and universities; expenditures on research and development; the number of patents granted to local organizations; and the level of venture capital investments. The authors maintain that the index is weighted to assess the quality of an area's "innovation infrastructure" and its "innovation capacity." Ahead of San Diego in the overall rankings are the San Francisco Bay Area, Austin, TX, Seattle, WA, and Raleigh-Durham, NC. Just behind are Washington, D.C., Denver, CO, Boston, MA, and Salt Lake City, UT.

[13] Precisely where and how the indirect benefits of high-tech activity will appear and accumulate remains uncertain. For example, while 'new economy' businesses boomed in San Diego during the 1990s, corporate support of the arts declined. This trend prompted Alan Ziter, executive director of the San Diego Performing Arts League, to write in a newspaper opinion piece: "Just as San Diego's arts and culture organizations are challenged to achieve creative excellence, we challenge San Diego's business community to match the commitment of funding made by their counterparts in other leading cities." Ziter attributes the funding tail-off to the disappearance of older, established, and reliable corporate sponsors. The 'agile,' 'lean,' and relatively small high-tech newcomers have yet to pick up all of the slack. See Alan Ziter, "Linking Business and the Arts in San Diego," San Diego Union-Tribune, October 31, 1999.

Southern California complements to Silicon Valley.[14] In the case of the life sciences, they hope that industrialists will be able to establish a permanent, self-sustaining "Biotech Beach."[15] And well aware of initiatives in other states to lure biotech companies away from their present bases of operation, San Diegans have jealously guarded these promising economic resources. During the city's 1992 mayoral race, the Republican candidate (Susan Golding) and the Democratic candidate (Peter Navarro) both declared commitments to assisting and retaining high-tech industries, and the biomedical industry in particular. A newspaper report on the two campaigns quizzed readers: "Who said the following? 'We must concentrate on keeping existing businesses in town. Biomedical and biotechnology firms are the keys to San Diego's economic future. Red tape and regulation are strangling commerce.' Susan Golding? Peter Navarro? The answer is both."[16] Julie Meier Wright, President and CEO of the San Diego Regional Economic Development Corp., remarked, "Our goal is to be

---

[14] See San Diego Regional Chamber of Commerce, State of California Office of the Governor, California Technology Trade and Commerce Agency, San Diego Regional Technology Alliance, and BIOCOM San Diego, Taking Action for Tomorrow: San Diego Life Sciences Strategic Action Plan, San Diego, CA: San Diego Regional Technology Alliance, May 2003; John Griffing, Silicon Valley II: A Review of State Policy Development Incentives, Sacramento, CA: State of California Senate Office of Research, 1985.

[15] Rick Shaughnessy, "The Search for San Diego's New Economy / Recovery May Depend on New Players as the Traditional Industries Fade Away," San Diego Union-Tribune, June 12, 1994, p. A-1. The name 'Biotech Beach' has been trademarked by Biospace, Inc., a company that specializes in web-based products and information services to life science companies. The site of the local industry, the "spectacular palm-tree-lined coast" of San Diego County, has also been described as a tempting garden paradise; see Elizabeth K. Wilson, "Biotech Eden," Chemical & Engineering News 79, 10, March 5, 2001, pp. 41-49.

[16] Pat Flynn and Ray Huard, "Mayoral Rivals Echoing Policy / Golding, Navarro Seek Business Vote," San Diego Union-Tribune, September 21, 1992, p. A1. Golding won. She was re-elected in 1996, garnering 78% of the vote. Her pro-business policies drew consistently favorable reviews from executives in the local biomedical industry.

mindful of what we have...so we don't give these other states an opportunity to get their foot in the door."[17]

CLUSTERS

San Diego was once a relatively sleepy Navy town, largely dependent on tourism, small-scale manufacturing, and the aviation and aerospace segments of the defense industry for its economic livelihood. In the late 1980s and early 1990s, the end of the Cold War and the deepest recession to hit the state of California in fifty years finally closed the curtain on that era in the region's economic history. Deep cutbacks in the city's traditional strengths indicated that future growth would likely have to be sustained in other industrial quarters. Out of necessity, San Diego has now placed its bets on late advances in the sciences and in engineering. San Diego's business and government leaders have formulated an 'industry cluster' based approach to supporting and promoting economic growth.[18] Clusters are defined as groups of interdependent, export-oriented, wealth generating enterprises. SANDAG, the San Diego Association of Governments, has identified a number of these clusters as 'economic drivers' (i.e., industries that have the potential to form the economic base of a region and broadly support progress and growth in other sectors of a regional

---

[17] Thomas Kupper, "N.Y. Parley Highlights Grab for Biotech Plums / Areas Aim to Attract Burgeoning Industry," San Diego Union-Tribune, June 19, 1998, p. C1. See also Robert Macmillan, "Biotech: How to Steal a Culture," Washington Post, June 1, 2004; and Denise Gellene, "In Land of Biotech Giants, Visitors Seek a Bit of Turf," Los Angeles Times, June 1, 2004.

[18] See Michael E. Porter, Clusters of Innovation Initiative: San Diego, Washington, D.C.: Council on Competitiveness, Monitor Group, and ontheFrontier, April 2001; San Diego Association of Governments (SANDAG), San Diego Regional Employment Clusters: Engines of the Modern Economy, San Diego, CA: SANDAG/Source Point, May-June 1998 (updated 2001); and San Diego Association of Governments (SANDAG), Creating Prosperity: San Diego Regional Economic Prosperity Strategy, San Diego, CA: SANDAG, July 1998.

economy).[19] The biotech industry is one of these 'targeted' sectors, along with biomedical goods and services, telecommunications, computer and electronics manufacturing, defense and transportation manufacturing, software and computer services, business services, financial services, and environmental technologies.[20]

Among the targeted clusters, 'emerging' (young and rapidly expanding) high-tech industries like biotechnology are receiving special attention and support because they feature relatively high average wages. Per-capita income is one of the key measures that San Diego economists and policy makers are using to gauge the economic health of the city and the region. Elevating this figure has become a primary policy goal. By 1998, the average wage for workers in San Diego biotechnology companies had reached $53,000, second only to software and computer services ($63,534) among regional industry clusters.[21] The biotech field also hires workers with the highest levels of educational attainment, and provides employees with better health insurance, retirement, and additional employment benefits than most

---

[19] San Diego Regional Technology Alliance, Industrial Clusters in the San Diego Region, San Diego, CA: San Diego Regional Technology Alliance/SANDAG, n.d.

[20] Non-targeted clusters include tourism, entertainment and amusement, agriculture, horticulture, medical services, and recreational goods manufacturing. All other regional economic activity falls into a residual category – businesses that do not meet the firm density and interdependence, export, and wage criteria that define industrial clusters.

[21] SANDAG, San Diego Regional Employment Clusters: Export Driven, San Diego, CA: SANDAG/Source Point, May-June 1998, p. 8. The slope of the curve across the average high-tech organizational hierarchy is not reported, but the compensation of San Diego CEOs and other executives at the top of the heap is generous, newsworthy, and occasionally a subject of controversy. See Michael Kinsman, "Annual Executive Salary Survey: Top Area CEOs Average $342,000 – up 12.9%," San Diego Union-Tribune, July 27, 1993, p. C-1; Thomas Kupper, "Top Pay," San Diego Union-Tribune, June 30, 2002. Even before the Enron and WorldCom scandals became front page news, media reports of exorbitant compensation packages and, occasionally, executive misconduct, had begun to strain the trust of investors and consumers in corporate officials (and CEOs in particular). See Rob Walker, "Why Jack Welch Isn't God – Overvalued," The New Republic, June 11, 2001.

other regional industries.[22] This is an employment base that San Diego officials are eager to broaden.

Of course, critics are quick to note that many San Diegans are being left behind in the new high-tech economy. Working to help technology firms expand their operations is fine, they say, but they doubt that current policies designed to aid new 'knowledge-based' ventures will contribute to what they consider equitable distributions of the wealth that these companies create. Economists working for the labor-affiliated Center for Policy Initiatives, for example, argue that the region's political and economic focus on the development of high-tech industry will serve to reinforce and deepen existing social inequalities.[23] While recognizing the crucial importance of the targeted high-tech clusters for the region's economic future, they do not consider high-tech innovation a cure-all. They point out that jobs lost in the region's former defense manufacturing base have been replaced by more low-paying service sector positions than by relatively high-paying science and engineering positions. Of the new jobs created in San Diego during the 1990s, more were opened in the tourism industry (28,352), where the median annual income was below $13,000, than in any of the high-tech clusters. The number of new jobs created in targeted

---

[22] San Diego Regional Technology Alliance, Industrial Clusters in the San Diego Region, San Diego, CA: San Diego Regional Technology Alliance/SANDAG, n.d.

[23] Enrico A. Marcelli, Sundari Baru, and Daniel Cohen, Planning for Shared Prosperity or Growing Inequality? An In-Depth Look at San Diego's Leading Industry Clusters, San Diego, CA: Center on Policy Initiatives, 2000. For a general discussion of growing social inequalities in American high-tech centers, see Joel Kotkin, The New Geography: How the Digital Revolution is Reshaping the American Landscape, New York: Random House, 2000.

industries combined during this period totaled 36,794.[24] By 1998, the targeted clusters still accounted for only 18% of regional employment; 22% percent of jobs within them paid below $18,000 per year; and 15% offered no health insurance benefits.[25] The critics anticipate, in addition, that as emerging clusters mature, reductions in average salaries, benefits, and educational qualifications within them will eventually become trends, along with increases in temporary employment.

The cluster building approach is premised on the notion that high-tech development will expand opportunities for education, training, and earning for all segments of the regional population, and so, promote the general welfare.[26] The labor economists remain skeptical about forecasts of significant trickle-down flows. They believe that economic policies in San Diego, as elsewhere in the country and around the world, are enabling the rich to get richer, while the poor get ever poorer. They draw on an industrial location analysis for supporting evidence. The city's material inequalities can be mapped geographically. High-tech development has occurred largely in the affluent suburbs at the north end of the city. The new wealth generated

---

[24] Marcelli, Baru, and Cohen, Planning for Shared Prosperity or Growing Inequality?, p. 11. This represents a 31.8% increase in the cluster. A San Diego Association of Governments report, in contrast, reports only a 1% increase in 'visitor industry services' cluster employment – a total of 390 jobs – during the same period. See SANDAG, San Diego Regional Employment Clusters: Export Driven, San Diego, CA: SANDAG/Source Point, May-June 1998, p. 8.

[25] Marcelli, Baru, and Cohen, Planning for Shared Prosperity or Growing Inequality?, pp. viii-ix.

[26] As examples, local leaders point to efforts like Operation Pipeline, an educational program spearheaded by the San Diego Regional Economic Development Corp. Operation Pipeline involves San Diego schools, local colleges and universities, and a number of the area's successful high-tech businesses. Its objective is to provide a better educated workforce for local high-tech companies by 1) raising standards and improving science and math instruction in area classrooms; 2) informing high school seniors and their teachers about educational and occupational opportunities; and 3) increasing high-tech internships and job fairs. See "Pipeline May Produce Bumper Crop of Workers for Local High-Tech, Biotech Firms," San Diego Business Journal, August 10, 1998, pp. 13-14.

by high-tech enterprises is being concentrated there as well. Non-targeted industrial clusters and working class San Diegans continue to reside, by and large, in the city's relatively impoverished south end.[27] In order to alleviate existing poverty and social polarization in San Diego, and to prevent opportunity and resource gaps from growing further, the labor economists insist that broader investments in human capital are necessary. They urge that even greater flows of public and private monies be diverted from direct support of targeted clusters to education and job-training programs. Redoubled efforts must be made, they contend, to provide low-income, working class San Diegans with skills they will need to compete in the labor markets of the new economy.[28] They also recommend the implementation of costly "shared prosperity standards" that would encourage higher wages, greater employment benefits, more full-time employment, unionization, and race and gender equity across all industrial sectors.[29] Attached to these recommendations is a warning and an appeal to the interests of San Diego's planners and industrialists: the burden of poverty will

---

[27] Marcelli, Baru, and Cohen, Planning for Shared Prosperity or Growing Inequality?, p.48.

[28] Mary Lindenstein Walshok, a San Diego educator and proponent of academic contributions to knowledge-based commerce, concedes that "[t]he lack of basic education and workplace skills among significant numbers of poor and minority groups needing to find useful work in a fast-paced, technology-driven economy is sobering indeed." She suggests that the universities that create the knowledge that drives high-tech innovation may also be able to contribute simultaneously to economic growth and the welfare of poor and minority communities by creating knowledge about how more effectively to train a high-tech workforce: "Alternative economic development strategies sensitive to the histories and the distinct character of inner-city and ethnic groups need research and evaluation. Expanded research on the relative effectiveness of culturally sensitive approaches to teaching and learning may be in order." See Mary Lindenstein Walshok, Knowledge Without Boundaries: What America's Research Universities Can Do for the Economy, the Workplace, and the Community, San Francisco, CA: Jossey-Bass, 1995; pp. 112-114.

[29] Marcelli, Baru, and Cohen, Planning for Shared Prosperity or Growing Inequality?, p. 59-65.

eventually become an impediment to regional growth and a drag on the development of high-tech clusters.

In response to these arguments, the official line of regional governments and business leaders is pragmatic. They counter that, as perfect as San Diego's climate may be, residents of the city do not live in a perfect world. They insist that policy makers must play the hands they are dealt, and that the principal challenge faced now by San Diego is the reconstruction of a sound economic base. They have concluded that, given the limited resources available for the promotion of regional development, San Diego's many communities and neighborhoods will be best served by enabling new high-tech industries to realize their potentials for growth. The creation of good jobs in these fields has become the first priority of San Diego's economic planners. Julie Meier Wright, head of the San Diego Regional Economic Development Corp., wards off criticisms about the narrowness of the cluster support strategy by reiterating the new economic reality: good manufacturing jobs are gone and "they're not going to come back."[30] She, in concert with many like-minded observers, advises the continuing formulation of policies that will aid industries with the capacity to deliver quality replacements. The faith of San Diego's economic and political elite has been placed in the market and high-tech innovation. For the powers-that-be, there is no viable alternative to lending full and unconditional support to new high-tech industries. They optimistically advertise the creation and expansion of high-tech

[30] Thomas Kupper, "Most San Diegans Not Benefiting From High-Tech Boom, Study Finds," San Diego Union-Tribune, September 21, 2000.

enterprise as a means of achieving prosperity and improving the conditions and quality of life of all San Diegans.[31]

In traditionally conservative San Diego, this view is by far the dominant one. Drowning out the voices of those who believe that staying the course will mainly benefit the 'new rich' at the expense of San Diego's working class are waves of daily press releases touting the wonders of high-tech invention and the financial rewards of high-tech commerce. Nevertheless, there is a broad consensus that spans both sides of the political fence. All agree that no matter how the pie is sliced, the growth and development of high-tech businesses will be a critical component in the economic life of the city in the 21st century. As it stands, San Diego is now purposefully attempting to transform itself into a vibrant Mecca for emerging high technologies.[32] Sanguine commentators envision the area as a 'technopolis,' a booming post-industrial 'region of innovation' nourished by participation in knowledge-based commerce around the Pacific Rim.[33] The city has made significant progress toward this goal, and is now regarded by others as a model for generating wealth and managing transitions and

---

[31] SANDAG, Creating Prosperity: San Diego Regional Economic Prosperity Strategy, San Diego, CA: SANDAG, July 1998.

[32] Or, as an anonymous staff writer for The Economist colorfully describes places of this kind, a high-tech "Nerdistan." See "Place Matters," The Economist, November 9, 2000.

[33] See "San Diego: Futureville," The Economist, February 3, 1996, pp. 20-21; Edward J. Blakely, "The Citistate of the Pacific Rim," Working Paper #598, Institute of Urban and Regional Development, University of California at Berkeley, 1993. See also, for general discussions, Manuel Castells and Peter Hall, Technopoles: The Making of 21st Century Industrial Complexes, London: Routledge, 1994; David V. Gibson, George Kozmetsky, and Raymond W. Smilor, eds., The Technopolis Phenomenon: Smart Cities, Fast Systems, Global Networks, Lanham, MD: Rowman & Littlefield, 1992; Allen J. Scott, Technopolis: High-Technology, Industry, and Regional Development in Southern California, Berkeley, CA: University of California Press, 1993; Raymond W. Smilor, George Kozmetsky, and David V. Gibson, Creating the Technopolis: Linking Technology, Commercialization, and Economic Development, Cambridge, MA: Ballinger, 1986.

reorientations in the global economy.[34] The development of biotechnologies is just one aspect of the city's current economic restructuring plans, but policymakers perceive it to be a crucial one.[35] In terms of generating wealth and contributing to industrial renewal in years to come, the possibilities for the city's cluster of biotechnology companies appear to be unmatched. So large and lucrative are markets for pharmaceuticals that a few successes in this area could offset a host of failures.[36]

Should fortune shine on San Diego as dependably as the sun, biotechnologies may well facilitate the transition of the city's economy from its modest manufacturing and defense contracting past to a prosperous future (for at least some) based on decentralized technological innovation. By the turn of the century, over 200 young biotechnology companies were operating locally (and roughly a fifth of these were publicly traded).[37] The Greater San Diego Chamber of Commerce reported in 1999

---

[34] Policymakers in Philadelphia, for example, have commissioned a 'reconnaissance' of San Diego, in hopes of discovering the secret to its success. See Basil J. Whiting, Greater Philadelphia First, Reports on the Competition: "San Diego: Technology's Perfect Climate", Philadelphia, PA: Greater Philadelphia First, 2002. See, also, McKinsey & Co., "Strategy to Accelerate Technological Growth in Houston," Houston, TX: Houston Technology Center, April 4, 2000.

[35] SANDAG, San Diego Regional Employment Clusters: Export Driven, San Diego, CA: SANDAG/Source Point, May-June 1998.

[36] A 1997 report released by the U.S. Department of Commerce forecast that the global market for bioengineered medical products could exceed $28 billion by 2006. See John Paugh and John C. Lawrence, Meeting the Challenge: U.S. Industry Faces the 21st Century: The Biotechnology Industry, Washington, D.C.: U.S. Department of Commerce, Office of Technology Policy, 1997, p. 34. In 2000, IMS Health, a health care market research, business analysis, and forecasting service, estimated the total worldwide pharmaceutical market at $317 billion. With most populations in the world either growing in number or aging, demand will almost certainly increase, and the size of the global market will expand still further with introductions of new therapies for conditions that now lack effective treatments.

[37] Thomas Kupper, "Biotech Businesses Abound But Breakthroughs Scarce," San Diego Union-Tribune, June 25, 2001; Bioscience Directory, 1998 San Diego County Edition, La Jolla, CA: Technology Director Publishing, 1998.

that the number of people finding employment in these firms had surpassed 25,000.[38] The notion of a permanent 'Biotech Beach' in San Diego is beginning to look increasingly like a reality. The economic impact of the life sciences in the city and the region over the past twenty-five years has been significant, and it is still growing.[39] Only time will tell, but the biomedical industry in San Diego will perhaps play a central role as the city attempts to reinvent itself in a high-tech mold.

Beyond stating the value of participation in the 'new economy,' industrialists and civic leaders in San Diego are able to make a further plea to encourage public support of the local biotechnology industry. To counter academic attacks on the political economy of pharmaceutical innovation, growing public skepticism about the risks of genetic research and engineering (particularly in agricultural applications), and growing concerns about ethical dilemmas associated with genetic testing, cloning,

---

[38] "High Tech Employment Here Climbs to a Record 110,300," San Diego Union-Tribune, September 23, 1999.

[39] In addition to 'biotech' companies conducting R&D on therapeutics and diagnostics, the blossoming of the biomedical industry in San Diego County has featured the formation of many other ventures that provide a broader array of scientific and medical goods and services. These companies manufacture, among other things, medical devices of various kinds, laboratory instruments and appliances, hospital equipment and supplies, and chemical and biological reagents for scientific and clinical use. Other firms perform pre-clinical and clinical contract research; several operate specialized contract manufacturing and packaging facilities, and still more offer scientific, regulatory, and business consulting services. When these enterprises are included, the employment figure for the San Diego biomedical industry rises to more than 32,000, by some estimates. See Thomas Kupper, "Biotech Businesses Abound But Breakthroughs Scarce," San Diego Union-Tribune, June 25, 2001; Bioscience Directory, 1998 San Diego County Edition, La Jolla, CA: Technology Directory Publishing, 1998. Not tallied in these counts are life science personnel working at the University of California, San Diego, San Diego State University, and the city's various non-profit research institutes that conduct biological studies. Also unaccounted for are numerous financial, marketing, advertising, publishing, law, architecture, construction, and real estate firms that orient their professional and technical services to the needs of biomedical community. For lists that illustrate the number and diversity of organizations involved in the local biomedical industry, see the membership and sponsorship rosters of BIOCOM, San Diego's local bio-trade association, at http://www.biocom.org; UCSD CONNECT, a University of California, San Diego extension office that works to promote the transfer and entrepreneurial commercialization of the university's intellectual properties, at http://www.connect.org; and the San Diego Regional Technology Alliance, at http://www.sdrta.org.

stem cell research, and the commercialization of biological knowledge,[40] they are proud to remind detractors that the city's new biotech companies are attempting to improve health and develop cures for dread diseases. When new biopharmaceuticals are introduced to health care markets, they are made available at steep prices, naturally, because the costs of drug development, testing, production, and marketing are immense. But if biotech companies can invent and manufacture effective remedies for ailments like cancer, heart disease, diabetes, AIDS, Alzheimer's disease, and so on, many consumers will consider them bargains, no matter what the cost. As Dick Murphy, the mayor of San Diego, says: "There is no doubt that our local biotechnology companies contribute enormously to our city's economy. But the work that they do means far more than just dollars and cents. . . . For many, it means the difference between life and death."[41] San Diego is becoming widely recognized as a model for industrial development and wealth creation in the 'new economy.' It is also becoming known around the country and the world as a center of basic and applied

---

[40] Until the late 1990s, most public opposition to GMOs (genetically modified organisms) was found in Europe; the American public remained relatively indifferent. In recent years, however, consumer advocates, environmentalists, and some scientists in this country have begun expressing concerns and raising questions regarding the adequacy of regulatory oversight in agricultural biotechnology, the uncertainties and risks associated with the release of GMOs into 'natural' environments, and the safety of genetically modified foods. Consequently, although agricultural biotechnology is well-established in this country, U.S. foodmakers and farmers have begun backing away from the use of bioengineered products, and the agbiotech industry is facing a potentially serious crisis. Bioengineered foods have been banned in many overseas markets, and domestic markets could begin to shrink as well. Dr. Henry Miller, senior research fellow at the Hoover Institution, goes so far as to say: "Food biotech is dead. The potential now is an infinitesimal fraction of what most observers had hoped it would be." For a summary of the issues and a history of the controversy, see Kurt Eichenwald, Gina Kolata, and Melody Petersen, "Biotechnology Food: From the Lab to a Debacle," New York Times, January 25, 2001. Biopharmaceutical developers have managed to steer well clear of such controversies.

[41] Penni Crabtree, "Biotech Seeks to Upstage Protests," San Diego Union-Tribune, June 22, 2001.

biological research – a pharmacological laboratory, a place where marvelous medicines may be invented.

HYBRITECH

To relate the story of San Diego biotechnology, I focus on the professional biographies of a relatively small group of people, nearly all with advanced training in the life sciences, whose paths crossed in the city at a small monoclonal antibody company called Hybritech.[42] Hybritech was founded in 1978, just as the business of biotechnology was beginning to take shape. It was San Diego's first so-called 'biotech' firm. The entrepreneurs who provided the spark for this start-up were Ivor Royston, a University of California, San Diego immunologist, and his lab technician, Howard Birndorf. Royston and Birndorf planned to manufacture antibodies that could be used to diagnose and treat human diseases. Hybritech was financed by Kleiner, Perkins, Caufield & Byers, a successful Menlo Park venture capital firm. In the beginning, this group put in $300,000, enough for Royston and Birndorf to set up a laboratory and an office, hire a small staff, and commence work. As the company grew, the founders recruited teams of capable scientists from high-profile universities and research institutions and experienced research managers from large pharmaceutical companies. These people were attracted by, among other things, the

[42] Monoclonal antibodies are made by fusing mammalian B-lymphocytes (antibody producing immune system cells) with myelomas (malignant bone marrow cells) that replicate indefinitely. The resulting hybrids, like their lymphocyte parents, secrete monospecific antibodies that react to particular antigens (immunogenic substances, a bacterium or a virus, for example) in very precise ways. Because these hybrid cells, called hybridomas, are 'immortal' (cancerous), they can be maintained in culture for extended periods, and large quantities of antibody can be harvested from them continuously. Hybridoma techniques were first developed in Cambridge, England, in 1975, by Georges Köhler and César Milstein. The pair were awarded a Nobel Prize for this work in 1984. Chapter five provides an explanation of hybridoma technology, the production and uses of monoclonal antibodies.

opportunity to develop a cutting-edge biotechnology with resources superior to those available in universities, by the business challenges of making a start up company work, and by options to purchase stock in the company at very low prices. Hybritech's R&D operation quickly put monoclonal antibody based diagnostic products on the market, and the company expanded rapidly. Hybritech went public in 1981, and, in 1986, was purchased by Eli Lilly for a reported $374 million.[43] At the time, it was the largest price that had ever been paid for a company in San Diego County. In terms of return on investment, Hybritech had been wildly successful.

Hybritech's career as an autonomous organization was important, not only for its shareholders and for San Diego, but also for the business of biotechnology at large. As one of the first and most successful companies to emerge in the nascent industry, Hybritech's achievements helped to validate biotechnology as an operative sector of the pharmaceutical trade. The company was a rarity among early biotech start-ups – within five years of its founding, it could boast of product revenues and profitability. As Robert Teitelman observes, Hybritech established early on "a reputation for going first-class, of doing things right." It utilized "high powered science" and "combined an entrepreneurial flare with a businesslike aura." In 1981, the year the company went public, Hybritech "may have been," says Teitelman, "the most viable biotechnology

[43] "Eli Lilly sweetens bid for Hybritech to $374 million," Wall Street Journal, December 18, 1985: 14W. The structure of the deal, and the valuation of Hybritech within it, was complicated. Estimated price tags as high as $480 million have been reported. Hybritech's stock was valued, in principle, at $32 per share. Shareholders could elect to receive cash, convertible notes, warrants to purchase Lilly stock, or contingency payment units based on Hybritech's future performance. See Hybritech-Eli Lilly Proxy Statement-Prospectus, February 14, 1986; Tim Knepp, "Eli Lilly's Inventive Contingent Payout Proves a Good Prescription for Hybritech," Buyouts & Acquisitions 5, 2 (May-June), 1987: 10-15, 37; Casey S. Opitz, "Hybritech Incorporated," Darden School Case #F-0793, Charlottesville, VA: University of Virginia Darden School Foundation, 1988.

firm going."[44] For a time, Hybritech, and a few other biotech firms making substantial commercial progress, subdued skeptics who believed that the efficacy of biotechnologies had been oversold. But the sale of the company to Eli Lilly also signaled to the giants of the industry that the time had come for them to bring their financial and organizational muscle fully to bear on the development of biotechnologies.[45]

The large corporations had initially adopted a 'wait and see' attitude regarding biotechnologies, letting others shoulder the financial burdens of research on these new and unproven tools. Most began, in the early 1980s, to dabble in molecular biology in their own laboratories, and to support inquiries in smaller firms through contract research and product licensing agreements. Still, the scale of these investments was relatively modest.[46] By the middle years of the decade, however, Hybritech and other start-ups had established clear-cut technological leads in a number of specializations (e.g., hybridoma technology and recombinant DNA). For all the advantages of size,

---

[44] Robert Teitelman, Gene Dreams: Academia, Wall Street and the Rise of Biotechnology, New York: Basic Books, 1989, p. 77.

[45] Ernst & Young, LLP has maintained a number of quantitative indices to chart the health of the biotechnology industry. One of these (no longer reported) was the Merck/Biotech Index. This measure illustrated the disparities in size among small biotech companies and the large pharmaceutical corporations. It compared Merck – for many years, the largest single drug manufacturer in the world – with the biotech sector as a whole. In 2000, Merck's product revenues totaled $40.4 billion; all biotech companies combined brought in $25 billion. Merck's net income was $6.8 billion; the biotech sector lost $5.8 billion. Merck's market capitalization was $146.5 billion; all public biotech companies (more than 300) were valued, in sum, at $330.8 billion. (Two years earlier, however, Merck's market value was $162 billion while that of all public biotech companies combined totaled only $97 billion). In 2000, Merck alone employed 69,300 people, while the entire biotech sector employed 174,000. See Scott W. Morrison, and Glen T. Giovannetti, Biotech '99: Bridging the Gap; 13th Biotechnology Industry Annual Report, Palo Alto, CA: Ernst & Young LLP, 1998, p. 7; Focus on Fundamentals: The Biotechnology Report, 15th Annual Review, Palo Alto, CA: Ernst & Young, LLP, 2001.

[46] See Martin Kenney, Biotechnology: The University-Industry Complex, New Haven, CT: Yale University Press, 1986, ch. 9.

the big houses could not expect to duplicate these advances on their own. They had bundles of cash and manufacturing and marketing prowess, but the small companies possessed the requisite scientific skills. The high price paid by Lilly for Hybritech served to confirm the legitimacy of the upstarts' new technologies as tools of drug development. And when Eli Lilly moved, the rest of 'Big Pharma' could no longer risk being left behind. Of the Lilly-Hybritech merger, Peter Drake, an industry analyst with Kidder, Peabody & Co., said at the time: "The key question the deal raises to pharmaceutical executives is not what is it going to cost them to get in, but rather what will it cost if they don't."[47] Many observers believed that the merger had sounded the death-knell for bioscience entrepreneurs. They anticipated that the giants of the industry would soon gobble up the puny upstarts.

DAVIDS AND GOLIATHS

The Hybritech sale did, indeed, give biotech entrepreneurs and investors a sobering indication of just how rough the sledding might become for small concerns attempting to go it alone. In the late 1970s and early 1980s, entrepreneurs and investors alike had been optimistic that biotechnologies could revolutionize the pharmaceutical industry by supporting the development of fully integrated, self-sustaining drug companies (i.e., firms that independently manage research, product development, regulatory affairs, manufacturing, marketing, distribution, sales, and other functions). Only a handful of biotech companies have approached this status.

[47] Ellyn E. Spragins, "Lilly and Hybritech: The Chemistry Looks Right," Business Week, October 14, 1985: 104D.

Amgen, located in Thousand Oaks, California, is perhaps the leading example.[48] Although a major scientific breakthrough can propel a new start-up into the stratosphere of multi-billion dollar companies, the process of biopharmaceutical development has proved extremely difficult, lengthy, and expensive, making this scenario seem increasingly unlikely for most biotech firms. As means of streamlining the process of drug discovery and testing, biotechnologies have not yet demonstrated their superiority to conventional methods. In the early 1980s, it became apparent that new biopharmaceuticals would become marketable only after passing through long and costly phases of discovery, development, and testing. Since then, industry observers have predicted that long before biotechnologies and bioengineered medicines finally transform the drug trade as promised, colossal corporations will have assumed proprietary control over most of them.

There are presently around 1500 biotech companies in the United States. Shares in more than 300 are traded publicly.[49] Most of these companies have yet to market products. Revenues in the biotech sector are still derived mainly from venture

---

[48] Amgen was founded in 1980. It currently possesses rights to five of the six top-selling bioengineered therapies on the market, including Epogen®, the leading revenue producer. See "Biotech by the Numbers," The Scientist, June 7, 2004; p. 49. Epogen is a recombinant form of erythropoetin (EPO), a protein made in the kidneys that is critical to red blood cell production. The substance is used to treat anemia in patients on dialysis. Amgen also benefits from high volume sales of another leading biological drug called Procrit®. Marketed by Ortho Biotech, a subsidiary of Johnson & Johnson, Procrit is a species of Amgen's recombinant EPO. It was approved for treatment of anemias related to the use of AZT and a wide range of chemotherapies and surgical procedures. Amgen licensed it to Ortho for sale in non-dialysis markets. In August 1997, an arbitrator determined that Ortho had violated the terms of the agreement. In May 1999, an Illinois Appellate Court upheld an earlier ruling that had ordered Ortho to pay additional royalties. See "Appellate Summary," Chicago Daily Law Bulletin, May 5, 1999, p. 1; and Amgen, Inc., Annual Report 1998, Thousand Oaks, CA: Amgen, Inc., 1999.

[49] Ernst & Young, Beyond Borders, the Global Biotechnology Report 2003, Palo Alto, CA: Ernst & Young LLP, 2003.

investments, public stock offerings, and corporate partnerships with larger pharmaceutical houses. The sector's net losses have not yet begun to recede. Its bottom line continues to be scrawled in red ink.[50] Only the top tier of biotech firms has achieved profitability. The vast majority of companies operate with alarming 'burn rates' (cash expenditures) and no income-generating products. Early stage start-ups have encountered periodic slumps in venture investing and in public equity markets, and while the catalogue of new biomedicines available to physicians has grown, so has the number of clinical failures mounted. Consequently, instead of attempting to compete head-to-head with industry behemoths, biotech firms have teamed with them in R&D collaborations. These alliances often involve equity participation. Small companies sometimes give away the store in exchange for the financial support they receive. For the larger drug companies, these arrangements have provided windows on new technologies. For many small biotech firms, they have been necessary as a matter of survival.[51] The costs associated with sustaining scientific progress are enormous. Until revenues from sales reach levels that can support research efforts, begging is a way of life for biotech executives. And while scientific and product development successes nudge biotech labs closer to profitability, they also turn them into attractive targets for takeovers by larger

---

[50] In 2002, the public companies in the biotech sector of the U.S. pharmaceutical industry lost $5.8 billion. See Ernst & Young, Beyond Borders, the Global Biotechnology Report 2003, Palo Alto, CA: Ernst & Young LLP, 2003.

[51] See Stephen R. Barley, John Freeman, and Ralph C. Hybels, "Strategic Alliances in Commercial Biotechnology," pp. 311-347 in Networks and Organizations: Structure, Form, and Action, eds. Nitin Nohria and Robert G. Eccles, Boston: Harvard Business School, 1992; Gary P. Pisano, "The R&D Boundaries of the Firm: An Empirical Analysis," Administrative Science Quarterly 35, 1990: 153-176; "The Governance of Innovation: Vertical Integration and Collaborative Arrangements in the Biotechnology Industry," Research Policy 20, 3, 1991: 237-249.

companies eager to extend or improve their development pipelines. In this environment, biotech firms cannot avoid dependence on capital supplied by corporate partners, and sometimes, when pinched, they are moved to surrender control of their intellectual properties.

In the years following Lilly's acquisition of Hybritech in 1986, 'Big Pharma,' as expected, steadily expanded its commitments to biological drug discovery.[52] Dreams of building start-ups into the next Merck or Pfizer largely evaporated. Many biotech companies were bred for eventual sale, and the Hybritech example provided a model for this strategy. Hybritech was among the highest of flyers in the early days of commercial biotechnology. By 1986, the company had amassed a sizable war chest to support its research. Still, the Hybritech braintrust feared that the firm would be unable, in the long run, to sustain its progress as an independent entity. The company had become profitable by manufacturing and marketing in vitro diagnostic kits, but investors were waiting on the development of in vivo imaging and therapeutic products. That was what Hybritech had advertised in its stock offerings, and that was where the big payoff was expected. But concrete results in this area, where the complexities of both biology and the regulatory approval process are magnified, appeared to be still a number of years away. The board of directors decided that the sale of the company would be the preferred means of honoring obligations to

---

[52] See Lynne G. Zucker, and Michael R. Darby, "Present at the Revolution: Transformation of Technical Identity for a Large Incumbent Pharmaceutical Firm After the Biotechnological Breakthrough," NBER Working Paper #5243, Cambridge, MA: National Bureau of Economic Research, August 1995; and Lynne G. Zucker, Michael R. Darby, and Marilynn B. Brewer, "Intellectual Capital and the Birth of U.S. Biotechnology Enterprises," NBER Working Paper #4653, Cambridge, MA: National Bureau of Economic Research, February 1994.

shareholders and supporting existing R&D projects. Teitelman lists Lilly's acquisition of Hybritech among a series of events that "marked the end of the heroic age of biotechnology, a loss of innocence, despite the profits that investors took home."[53] The career of the company as an autonomous organization thus had a significant impact on the development of the biotech field at large. Hybritech played an important role in establishing biotechnologies within the pharmaceutical industry, but the sale of the company also punctured some over-inflated hopes concerning the future prospects of small firms working to develop bioengineered drugs.

The long-awaited weeding of the weak and small from the ranks of independent pharmaceutical companies, however, has yet to occur in any widespread manner, and new start-ups continue to appear and to attract significant amounts of capital.[54] Brook Byers, the venturer who first seeded Hybritech, and later invested in many more San Diego life science companies, remarked in 1995: "I don't think predictions in this industry carry a lot of weight. Our sale of Hybritech to Lilly in 1986 started a wave of predictions concerning consolidations and mergers. That was nine years ago."[55] On the passing scene in the pharmaceutical business, size apparently still doesn't count for everything. Recent developments in the field have convinced some stock analysts and industry insiders that the biotech sector of the drug

---

[53] Robert Teitelman, Gene Dreams, p. 9.

[54] Bruce V. Bigelow, "Investment Cash Swings in Direction of Biotechs," San Diego Union-Tribune, July 30, 2002.

[55] Quoted in Kenneth B. Lee, Jr., and G. Steven Burrill, Biotech '96: Pursuing Sustainability, An Industry Annual Report, Palo Alto, CA: Ernst & Young LLP, 1995, p. 62. Predictions of the 'Great Shakeout' have a history nearly as long as the industry itself. See, for example, "Biotechnology – Seeking the Right Corporate Combinations," Chemical Week, September 30, 1981, p. 40.

business will yet be able to survive in something like its present form, with numerous small companies operating more or less independently. The success of these companies, they say, will not depend on the discovery of blockbuster drugs or the works of advertising, marketing, and sales armies, as is the case with the 'Big Pharma' corporations, but rather on innovation in specialized technological niches.[56] The free-standing biotech research and drug development enterprise, once widely considered an endangered organizational form, may yet become a permanent fixture in the pharmaceutical industry.

AN ENTREPRENEURIAL CULTURE

Again, surveying the history of Hybritech provides some lessons concerning this trend that defies what once, before the advent of 'post-industrial' trade and commerce, appeared to be cold and unforgiving economic logics. In the business of drug design and production, bioscientific techniques emerging from academic laboratories continue to be viewed as keys to the future, and they continue to present commercial opportunities to persons who possess the specialized knowledge and skills necessary to take advantage of them. Many of those who contributed to Hybritech's meteoric ascent in the late 1970s and early 1980s from a tiny lab and office to a multi-million dollar diagnostics manufacturer are such persons. At Hybritech, these individuals learned how to start and sustain a compact science-based enterprise, and to steer it through a competitive environment inhabited by powerful titans. In San Diego, Hybritech produced people who believe they can do big things with less. In the

[56] See, for example, Randall Osborne, "Genomics Will 'Fragment' Industry; Deconsolidation Wave Due Next," BioWorld Online, June 27, 2001.

present, they continue to try, and they are still persuading others that it can be done. Ted Greene, the company's CEO in its early years, refers to Hybritech as "a great training ground."[57]

Shortly after Hybritech had accomplished its initial objectives of inventing and marketing several profitable diagnostic products, its scientific and managerial teams began to generate ideas for new technologies and paths of research. For various strategic reasons, many could not be developed in-house. In 1983, Howard Birndorf, one of the original founders and then the firm's vice-president of business development, left Hybritech, along with Tom Adams, the company's head of product development, to start Gen-Probe, a DNA probe manufacturer. This was the first of many 'spin-offs' involving Hybritech personnel and technologies. After Hybritech was purchased by Lilly, this trend accelerated. Many of the key scientists and managers that had been recruited to Hybritech in its formative years with enticements of stock equity had become wealthy as the market value of the company soared. This allowed them to seek out new and more exciting opportunities when they became bored or otherwise disenchanted with changes in operations and direction instituted by Lilly management. As industry observer Jim McCamant notes, "Hybritech's purchase by Lilly freed up a lot of people who were entrepreneurial and who now wanted to do other things. Science has been in San Diego a long time, with UCSD and Scripps and

[57] UCSD CONNECT video, "Meet the Entrepreneur," May 1991.

Salk. Hybritech helped generate the venture people – people who said, 'Let's do that again.'"[58]

Just as these persons were exiting Hybritech, the startling returns that the company had delivered (and the phenomenal popularity of biotech stocks on Wall Street at the time – a response to similar success stories elsewhere) had investors flocking to San Diego like murders of crows. Venture capitalists came to size up the new entrepreneurs, and, in many cases, to supply them with millions of dollars with which to pursue their ideas. The Hybritech team dispersed, but all remained in San Diego. They remained in contact with each other, cooperatively taking advantage of many opportunities for reproducing their success with new sets of technical and commercial problems and goals in conducive scientific and financial environments. The members of the original Hybritech group have since played pivotal roles in the formation of more than fifty biotech and biomedical companies in the city of San Diego, and four venture capital firms, as well.

All of these enterprises – the 'begattings' of Hybritech – are located near Scripps, Salk, UCSD, and the academic bioscience research community. They reside within webs of personal and professional networks established by the Hybritech folk, and have grown by utilizing the collective scientific, financial, and managerial acumen that these networks embody and sustain. The Hybritech group was, and continues to be, so prolific, so well connected, and so central to the establishment and development of the biotechnology industry in San Diego that they have become known in local

[58] Quoted in Tom Gorman, "Business of Biotech Comes of Age in S.D." Los Angeles Times, May 26, 1991: A27-A28.

circles as the 'Hybritech Mafia.' Bill Otterson, late director of CONNECT, a University of California, San Diego extension office that offers a variety of services to local high-tech entrepreneurs, once called Hybritech the "granddaddy of San Diego biotech."[59] Among San Diego industrialists, the historical significance of Hybritech's legacy is widely recognized.[60] Much like the engineers who spawned Silicon Valley's semiconductor industry by spinning off companies from Fairchild Semiconductor Corporation,[61] persons departing Hybritech, Inc. to become involved in entrepreneurial ventures have played central roles in the development of San Diego's 'Biotech Beach.'

The number of companies registered, corporate partnerships negotiated, or dollars invested and earned by the Hybritech alumni can be readily charted. The full impact of this group's activities on the growth of the local biomedical industry is less calculable. Understanding the contributions that these individuals have made requires attention to the methods and practices that they employed to build Hybritech and its 'begattings,' and to the particular circumstances within which they operated. The Hybritech story deserves a place near center stage in the history of the biotechnology industry, not only because the company delivered spectacular returns, but also because

---

[59] UCSD CONNECT video, "Meet the Entrepreneur," May 1991.

[60] In February 1996, the Greater San Diego Chamber of Commerce sponsored a reception to honor the collective accomplishments of the Hybritech folk and their contributions to the San Diego business community. Several have received 'Legend' awards at the sponsored by BIOCOM, the local industry trade association.

[61] See Robert Kargon, Stuart W. Leslie, and Erica Schoenberger, "Far Beyond Big Science: Science Regions and the Organization of Research and Development," pp. 334-354 in Big Science: The Growth of Large Scale Research, eds. Peter Galison and Bruce Hevly, Stanford, CA: Stanford University Press, 1992; and AnnaLee Saxenian, Regional Advantage: Culture and Competition in Silicon Valley and

the persons responsible for its success went on to fashion collectively a culture of scientific entrepreneurship in the northern suburbs of San Diego.[62] Using Hybritech as a springboard, these individuals worked to transform the city into a place that fosters biotechnical innovation. In the course of practical personal and collective experience, the Hybritech folk learned how to shepherd biotech companies through the arduous process of attracting start-up money, recruiting and managing people and technologies, procuring necessary infusions of cash at various stages of maturation, organizing product developments, and negotiating legal and regulatory procedures and obstacles. As Hybritech's scientific and managerial teams devised reliable techniques for assembling resources and solving problems, flexible ways and means of handling these tasks became more or less conventionalized. And when spin-offs from the firm began to dot the landscape at the north end of the city, these strategies and practices were diffused, reproduced, and refined. To say that the Hybritech alumni invented the biotechnology industry in San Diego may be to exaggerate only slightly. By drawing together the various materials and forms of expertise required to make biotechnology companies work, they broke new ground. On the unfolding paths of their plans and actions, the Hybritech group established novel ways of conducting business and conducting science.

Route 128, Cambridge, MA: Harvard University Press, 1994, ch. 1-2; and "The Genesis of Silicon Valley," Built Environment 1983, 9: 7-17.

[62] Observing similar ways of doing business and science in Silicon Valley, Lee, et al. call this kind of environment a "habitat" for entrepreneurs. See Chong-Moon Lee, William F. Miller, Marguerite Gong Hancock, and Henry S. Rowen, The Silicon Valley Edge: A Habitat for Innovation and Entrepreneurship, Cambridge: Cambridge University Press, 2001.

The numerous biomedical companies in San Diego that can trace personal connections back to Hybritech represent only a part of the company's legacy. As many of Hybritech's executives and scientists moved from the 'parent' company to put together new firms, their activities gave rise to an institutional milieu in which money, managerial expertise, and technical skill circulate and are available to be organized and applied in practical entrepreneurial projects. Largely due to the efforts and successes of the Hybritech group, San Diego's commercial biotech community now features the resources – capital, know-how, and cooperation – necessary to support sustained high-tech innovation. Narrating the careers of the Hybritech crew is a way of explaining how this happened. Their personal histories have traversed critical events and episodes in the maturation of the San Diego biotechnology industry. Tracing their paths within this milieu leads one directly to times and places in which felicitous contacts, recruitments, and agreements were made, important formal or informal lines of communications were opened or utilized, consequential strategies were formulated or adopted, and vital knowledge, materials, and technologies were developed and transported from one time and place to another. Each of their stories represents a piece of a larger social mosaic that, when assembled, depicts the creation of an industry, the growth of a community, around the activities of what was, in the beginning, a very small group of innovators. This community has now grown large. It includes not only a population of discrete firms, but also an expanding infrastructure of supporting organizations and institutions. As the members of the Hybritech team pursued their objectives, they opened channels of communication and resource

distribution that consolidate a field of novel technical, managerial, and financial practices.

As this process has unfolded, competition in the industry has intensified. The complex problems of applying biotechnologies to commercial drug development have become more clearly defined through the efforts of researchers in both academic and corporate settings. Investors have become ever more sophisticated regarding the scientific uncertainties and financial risks that characterize the business. In sum, the conditions and demands of engaging in biotech entrepreneurship have evolved, and, in many ways, become more difficult. Yet, at the same time, methods and resources for tackling these problems have been developed and organized. Recounting the various ways in which these persons have contributed to Hybritech and its many 'spin-offs' provides a detailed portrait of how entrepreneurial actions have enabled biomedical research and industrial development to progress in San Diego. To tell tales of careers and companies, friendships and animosities, experiments and discoveries, decisions and deals, is to compose genealogies of scientific and managerial techniques, chronicles of organizational genesis and change, and to show how such histories are interrelated, dependent as much on chance and accident as purposive design, yet always the products of social interaction and human creativity.

The original founders, chief scientists, and managers of Hybritech were the 'scientific entrepreneurs' who set the San Diego biotechnology industry into motion. As these individuals have gone about their business, they have continued to draw new technologies and skilled persons to the city, expanding the supply of human and material resources that today comprises the lifeblood of the local industry. They have

worked to promote the growth and application of new knowledge and techniques in the life sciences, and they have shared their expertise with others in order to further the common interests of the local business community. The formation and expansion of the biotechnology industry in San Diego can be credited in large measure to their efforts and accomplishments. The story of the Hybritech alumni is not one of unqualified success. The players have experienced numerous frustrations and reversals of fortune, and witnessed many a plan come to naught. They have compiled an impressive record of achievements, but not without making what turned out to be mistakes and misjudgments along the way. Neither is their story one of perfect harmony. Their associations and projects have not, of course, been devoid of rivalries and rows. Like any family or community, the members of the Hybritech group have had their differences – amongst themselves, and with others. Effective teamwork has been an essential ingredient in their scientific and commercial collaborations, but, naturally, conflicts and quarrels have periodically disrupted these efforts. Still, for all the imperfections and inefficiencies that have characterized it, the rise of biotechnology in San Diego has been spectacular. Within the webs of association that have comprised and given shape to this field of action – this culture of scientific entrepreneurship – relationships that originated in and around Hybritech have been among the most important.

Hybritech itself is today defunct. The company never realized its promise and its ultimate goal following the sale to Eli Lilly – that is, it never produced a cancer therapeutic. When income from Hybritech's line of diagnostics products began to dip in 1994 and 1995, Lilly shut down the firm's in vivo R&D program and unloaded the

rest of the company to Beckman Instruments. According to unnamed sources cited by the Wall Street Journal, the price was less than $10 million.[63] All of the vigor and promise that characterized the company when it was a technological leader in its field had vanished, dissipated by competition and what many involved believe to be neglect and mismanagement by the Lilly brass in Indianapolis. Three years later, Beckman announced that it was splitting up Hybritech's manufacturing operations, moving pieces to Carlsbad, California, and Chaska, Minnesota.[64] The company retained just over 100 employees in San Diego. For holdovers from the firm's glory days in the early and middle 1980s – and there were a few – the deserted laboratories and quiet corridors of the company's remaining facilities must have had the sad, eerie feel of a ghost town.

A recent Forbes magazine report on the growth of high technologies in San Diego describes Hybritech today as "a mere historical footnote." The piece remembers rightly, however, that Hybritech supplied the city with a "nucleus of talent" that was critical to the formation of the local biotech industry.[65] In this social history of San Diego biotechnology, I describe how the Hybritech group came together, how they made Hybritech work, and how they later went on, taking the lessons of this experience, to start and direct many more life science enterprises in the city. In terms of contributing to the growth of San Diego's emerging high-tech

---

[63] See Thomas M. Burton and Rhonda L. Rundle, "Lilly Gets Out of Biotechnology and Medical Diagnostics," Wall Street Journal, October 2, 1995, p. B4.

[64] See "Beckman Coulter Consolidates," Orange County Business Journal, October 12, 1998, p. 4.

[65] Tim W. Ferguson, "Sun, Fun, and Ph.D.s, Too," Forbes 163, 11, 1999: 220-229.

economy, Hybritech did more than simply make money, generate jobs, and manufacture bioengineered health care products. It also manufactured scientific entrepreneurs. The objective of the research reported here has been to examine how these persons, acting cooperatively in order to establish Hybritech and numerous other companies, learned how to accomplish their entrepreneurial ends, and in so doing, fashioned new roles for biological researchers in the pharmaceutical business, effected significant institutional changes in science and industry, and helped to make San Diego a world-class center of commercial biotechnical research and development.

THE NUTS AND BOLTS OF SCIENTIFIC ENTREPRENEURSHIP

This dissertation, then, focuses directly on the practical technical and organizational work undertaken by scientific entrepreneurs as they founded new biotechnology firms in San Diego and established research and development programs within them. John M. Stewart, a veteran executive in the pharmaceutical industry, and a participant in the formation and operation of several biotech companies, has remarked: "If there is any area in which a great contribution could be made to the understanding and fostering of entrepreneurship, it is in the range of activities that a principal organizer must undertake in creating a new venture."[66] This work is intended as a contribution of this kind. It is not my aim here to promote entrepreneurship. I am simply reporting on the forms it has taken in San Diego's biomedical community. But I will describe in detail the activities that have comprised successful entrepreneurship in biotechnology, the particular circumstances in which

[66] John M. Stewart, "Capitalizing on New Opportunities: Entrepreneurship in Biotechnology," pp. 23-37 in The Business of Biotechnology: From the Bench to the Street, ed. R. Dana Ono, Boston, MA: Butterworth-Heinemann, 1991, p. 26.

these activities were engaged, and the outcomes of these collective pursuits. This study narrates the technical and social changes that biologists, biochemists, physicians, and other researchers (along with their financial partners) have produced as they have ventured beyond the academy and established pharmaceutical companies with their new tools. The following questions frame the empirical core of this dissertation:

- What is the substance of scientific entrepreneurship? How do bioentrepreneurs go about the business of putting together biotechnology companies and guiding them through their start-up phases? What kinds of knowledge and skill are required for these tasks, and where do entrepreneurs acquire them?
- How do bioentrepreneurs assemble the various resources that nourish innovative life science companies? How do they attract capital and recruit scientists, technicians, and managers? How do they represent potential risks and rewards to others? How do they persuade people to invest or collaborate?
- What are the genealogies of entrepreneurial biotech ventures? How do new 'spin off' firms emerge from within 'parent' companies or research institutions? What skills, techniques, and economies of work are transferred within a genealogy? How are they transferred?
- What are the political, legal, and institutional support structures upon which life science entrepreneurs depend, and how do they attempt to secure these requirements within emerging 'technoregions?'
- How did the involvement of bioscientists in entrepreneurial endeavors – something once quite unusual – become conventional?[67]

To answer these general questions, I focus on the situated, concerted, and inventive actions of particular individuals. I claim in this dissertation (and in opposition to many social scientific theories discussed in the next chapter) that persons rather than abstract economic, technological, or institutional 'forces' determine outcomes in large-scale social processes. At the center of my account are the

[67] Steven Shapin deserves credit for this summary of research topics.

professional biographies of a select group of scientific entrepreneurs, persons who have played prominent roles in the formation of the biotech community in the city of San Diego. The story that I tell is about the opportunities for economic and medical progress that these persons identified – or, indeed, created – and how they sought to take advantage of them. The empirical chapters of this work document how these individuals learned, through practical personal and collective experience, the art of high-tech entrepreneurship and how, in the process, they invented new economic and scientific spaces. What emerges is a portrait of scientific entrepreneurship as a thoroughly social phenomenon. The emphasis in this story, however, unlike many of the classic sociological statements on entrepreneurship,[68] is not so much on the ways in which an entrepreneurial culture has encouraged and supported entrepreneurial actions, but rather on the ways in which entrepreneurial actions have produced and animated an entrepreneurial culture.

Of course, the formation of the biotechnology industry took place within larger historical and institutional processes.[69] Among these can be included the development

---

[68] The writings I have in mind here include: Peter Berger, Brigitte Berger, and Hansfried Kellner, The Homeless Mind: Modernization and Consciousness, New York: Random House, 1973; Maurice H. Dobb, "The Entrepreneur Myth," pp. 3-15 in On Economic Theory and Socialism: Collected Papers, London: Routledge & Kegan Paul, 1955; Everett E. Hagen, On the Theory of Social Change: How Economic Growth Begins, Homewood, IL: Dorsey Press, 1962; David C. McClelland, The Achieving Society, Princeton, NJ: D. van Norstrand Co., 1961; Werner Sombart, The Quintessence of Capitalism: A Study of the History and Psychology of the Modern Business Man, trans. M. Epstein, New York: H. Fertig, 1967 [1915]; and Max Weber, The Protestant Ethic and the Spirit of Capitalism, New York: Charles Scribner's Sons, 1958 [1904-1905].

[69] For a cautionary note to planners who would reproduce the success of Silicon Valley in other regions by assembling or cultivating the basic ingredients ("entrepreneurial vision," "strong university science," "plentiful sunshine and even more plentiful government money") without taking into account the complex ways in which broader institutional structures and relationships at particular historical moments might influence local events, see Robert Kargon, Stuart W. Leslie, and Erica Schoenberger, "Far Beyond Big Science: Science Regions and the Organization of Research and Development," pp. 334-354 in Peter Galison and Bruce Hevly, eds., Big Science: The Growth of Large-Scale Research,

of the life sciences (and especially molecular biology) as technical specialties and as academic disciplines, the historical trajectories and interrelations of academic and industrial research, patterns of federal funding for biomedical science, the corporate structuring of the pharmaceutical and health care industries, the maturation of venture capital organizations, the local histories of cities and regions in which commercial biotechnology development has taken root, and the list goes on.[70] Localized appearances of new biotechnology firms in the 1970s were, to be sure, shaped significantly by events and processes unfolding 'at a distance' in time and space. But if broader structural movements prepared the ground for the emergence of this industry, they did not 'cause' it, nor determine the paths of development that the field has followed in particular times and places. The phenomenon of commercial biotechnology as it is known today was not, and could not have been, predicted. Structural accounts are insufficient if explanations are wanted of precisely where, when, and how the biotech industry took shape. Any account of why a particular region has become a major site of biopharmaceutical research and development in the present must include a description of how scientific entrepreneurs made it so.

Stanford, CA: Stanford University Press, 1992. The authors apparently assume, however, that 'entrepreneurial vision' is uniformly blind or insensitive to macroscopic historical conditions and trends that can affect entrepreneurial projects. Why this should be so is unclear. See also, Doreen B. Massey, Paul Quintas, and David Wield, High Tech Fantasies: Science Parks in Society, Science, and Space, London: Routledge, 1992, and Martin Kenney, ed., Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, Stanford, CA: Stanford University Press, 2000.

[70] Chapters three and four of this dissertation include potted histories of these developments, and others, that comprise the prehistory of commercial biotechnology in San Diego.

METHODS AND METHODOLOGY

The origins of the entrepreneurial resources found in San Diego's biotech community – the scientific skills, the business acumen, the managerial talent, and organizational know-how – are as scattered and diverse as the backgrounds and histories of the individuals who work in this place. These resources flow through and are coordinated within social organizations and social networks, but they are, of course, embodied in individuals. Individuals lend unique talents and skills to corporately managed projects. These capacities are acquired and refined in the course of practical experience and activity. Personal histories, then, are significant in the making of innovations, and, in social and historical studies of innovations, biographies deserve empirical attention. In this work, I try to give them their due. This dissertation is based, to substantial degree, on biographical research. By biographical research, I do not mean hagiography or the study of personalities – this is not a tale of 'great men,' heroes, visionaries, or inventive geniuses. At the same time, I do not mean to exclude attention to actions that people, in everyday language, associate with a person's character or temperament, or to the uniquely creative contributions that individuals make to processes of innovation.

In sociological accounts, there is always a balance to be struck between the individual and society. When treated judiciously, and in accord with established sociological grounds of inference,[71] biographies can serve as windows on social

[71] The specific grounds of inference to which I refer here are of the kind presupposed by Howard Becker in his discussions of culture, that is, practical generalizations concerning the ways in which people 'do things together,' and against which the particulars of social life are made intelligible. See Howard S. Becker, Doing Things Together, Evanston, IL: Northwestern University Press, 1986, ch. 1.

processes. Marxist historian Robert M. Young emphasizes the contextualizing aspects of biographical studies to recommend them: "Biography is human nature on the hoof, embedded in lived contradictions, replete with meditations and articulations of social, familial, and historical life."[72] Historian of science Charles Rosenberg makes the point in this way: "Although every life is idiosyncratic, no life is random; every life course reflects a specific configuration of social options."[73] Human beings are fundamentally social. They live together. It is very difficult for them to survive otherwise. So, while individuals make choices, they do so among others, and not necessarily, to paraphrase Marx, under conditions of their own choosing. To learn about individuals, and their choices, and the lives they lead, is, of course, to learn about their times and places as well.

Following individuals through a society or a culture is a way of learning what that society or culture is like. I retrace the paths of entrepreneurs in San Diego's biotech community, and compose chronicles of things they did together in order to convey a sense of what this industrial ecology is like, and, further, to illuminate the work that these persons did to create it. The objective here is to locate individuals and their activities in larger social and historical contexts. In the case of biotechnology, these contexts can be defined as particular streams of scientific and industrial development (i.e., particular social organizations and social networks – or, to be more precise, plural associations of empirical interest as they take shape over time).

---

[72] Robert M. Young, "Biography: The Basic Discipline for Human Science," Free Associations 11, 1988, pp. 108-130.

[73] Charles Rosenberg, "Science in American Society: A Generation of Historical Debate," Isis 74, 1983, p. 365.

Research on personal histories can be employed as a means of investigating how individuals come to meet and work together in order to engineer social and technological change, and how they get on with the business at hand.[74] Scholars in science and technology studies sometimes compose biographical accounts, but typically, when technological innovations are at issue, it is the design and diffusion of particular artifacts or techniques that receive special historical and ethnographic attention. These works are often more concerned with social histories of things than with social histories of people (perhaps naturally, since they have typically been undertaken to refute 'technological determinism,' and to demonstrate that technologies and technological systems do, in fact, have social histories that are not trivial).[75]

Biographical research about people can supplement accounts of this kind, and broaden understandings of scientific and technological change, by drawing attention to relevant situations and social processes removed in time and space from innovations of particular interest. Studies of individual careers can tell where innovators come from, how they happen to find themselves in situations where they can make innovations, and how they became people who were able to do so. They can be used to identify the paths that people follow to the specific locales and circumstances from which innovations emerge. Knowing about these paths and the people who travel on them is important when the goal of research is understanding just how and why innovations appear in particular forms, in particular times and places. Focusing on the

---

[74] Of course, sociologists need not produce biographies with kind of detail that historians customarily include in order to benefit from the exercise.

[75] See, for example, Lorraine Daston, ed., Biographies of Scientific Objects, Chicago: University of Chicago Press, 2000.

histories of persons in addition to those of organizations, artifacts, or technological systems is a means of further exploring 'sociotechnical' networks.

This study employs historical and ethnographic methods. It is based primarily on intensive interviews with persons who participated in the establishment of the biotechnology industry in San Diego – the founders of Hybritech and its 'spin-offs,' key members of the scientific and managerial teams that were recruited to these companies, and others who have played significant roles in the development of local enterprises. These include, for example, venture financiers, and other investors, board members, persons affiliated with local trade associations and various supporting organizations that provide professional services to high-tech entrepreneurial ventures, and faculty and administrators at the universities and research institutions from which local firms have recruited personnel and technologies. In all, fifty-two interviews were conducted, ranging from thirty minutes in length to one hundred and twenty minutes. The personal accounts and recollections gathered in the interviews have been used to construct histories of entrepreneurial careers, projects, and companies in San Diego biotechnology.

Erica Shoenberger calls this method 'corporate interviewing.'[76] It is useful and appropriate in the sociological study of industrial organization because, as Schoenberger describes, it enables the analyst "to understand [a] firm's observed behavior (regarding, for example, its locational strategies), in light of the firm's own history and circumstances and in the context of other considerations such as the firm's

[76] Erica Schoenberger, "The Corporate Interview as a Research Method in Economic Geography," Professional Geographer 43, 2, 1991: 180-189.

competitive strategy, relationship to its markets, product technology, labor relations, the behavior of competitors, and the like."[77] It also affords insight into the interactions and practical works that concretely make up a firm's operations and strategic maneuverings. The corporate interview is a method well suited for exploring a broad range of issues related to the formation of 'industrial ecologies.' It affords access to the diverse and dynamic social interactions that constitute such organizational fields. Despite limitations, it has, as Schoenberger goes on to say, "the merit of recognizing that firms are institutional agents embedded in a complex network of internal and external relationships. They [firms] are populated by individuals faced with a myriad of constraints and possibilities that are difficult, if not impossible to disentangle [with quantitative methods].... The loss of statistical generalizability brings into greater relief the real-world predicaments and strategies of these institutional agents."[78]

THE TRUTH ABOUT COMPLEXITY

This dissertation is an account of real-world events. It aims to retain and convey a bit of the 'thickness' of the social and historical contexts in which the events took place. So, it is also a study of situated social interactions, and of social networks assembled and maintained through situated interactions. On the passing scene in sociology, network analysis is a trendy 'methodology.' High-tech industries, including biotechnology, have received considerable attention from network analysts

[77] Schoenberger, "The Corporate Interview," p. 180.

[78] Schoenberger, "The Corporate Interview," p. 181.

because of the innovative organizational forms that can be found within them.[79] According to Albert-László Barabási, a physicist intrigued by mathematical properties common to network phenomena of many different kinds (e.g., the internet, the transmission of communicable diseases, protein interactions within cells), scientific and economic progress in biotechnology is propelled by interfirm alliances, and so, the biotech industry offers "an unusually well documented case of network formation, allowing us to follow and understand the emergence of networks in economic systems."[80] Most works in this genre, however, apply the physicists' methods. They

---

[79] Albert-László Barabási, Linked: The New Science of Networks: How Everything is Connected to Everything Else and What It Means for Science, Business, and Everyday Life, Cambridge, MA: Perseus, 2002, p. 207. For other works that discuss the relationships between social networks, social organizations, and social complexity, see W. Brian Arthur, Increasing Returns and Path Dependence in the Economy, Ann Arbor, MI: University of Michigan Press, 1994; W. Brian Arthur, Steven Durlauf, and David Lane, eds., The Economy as an Evolving Complex System II, Reading , MA: Addison-Wesley, Series in the Sciences of Complexity, 1997; Philip Ball, Critical Mass: How One Thing Leads to Another, Farrar, Straus, and Giroux, 2004; Mark Buchanan, Nexus: Small Worlds and the Groundbreaking Science of Networks, New York: W.W. Norton & Company, 2002; Mark Buchanan, Ubiquity: The Science of History...or Why the World is Simpler than We Think, New York: Random House, 2000; Rob Cross and Andrew Parker, The Hidden Power of Social Networks: Understanding How Work Really Gets Done in Organizations, Boston, MA: Harvard Business School Press, 2004; Malcolm Gladwell, The Tipping Point: How Little Things Can Make a Big Difference, Boston: Little, Brown, 2000; Paul M. Hildreth and Chris Kimble, Knowledge Networks: Innovation Through Communities of Practice, Hershey, PA: Idea Group Publishing, 2003; Martin Kilduff and Wenpin Tsai, Social Networks and Organizations, London: Sage, 2003; Duncan J. Watts, Small Worlds: The Dynamics of Networks between Order and Randomness, Princeton: Princeton University Press, 1999; Duncan J. Watts, Six Degrees: The Science of a Connected Age, New York: W.W. Norton & Company, 2003.

[80] Barabási, Linked: The New Science of Networks, p. 207. For a critical review of the empirical evidence supporting the 'small world' thesis, see Judith S. Kleinfeld, "Could It Be A Big World After All? The 'Six Degrees of Separation' Myth," Society, 2002. It is possible that the network theorists are correct with qualifications and provisos, within certain circumscribed, empirically-defined parameters. Network connections may often fail to link distant persons (or 'nodes') in real-world social interactions, but the biotech industry may belong to a special class of social systems – systems that function in ways (or, to say it a bit differently, are characterized by social conventions) that enhance the integrity of network pathways.

attempt to map the architectures of social networks in the abstract, leaving the content and substance of network connections and associations unexamined.[81]

Social life is complicated. In fact, its complexity is overwhelming. Network analysis was developed as a technique for managing problems of complexity, but it is not designed to conquer them. Network analysts employing mathematical tools may be able to peel some layers off the onion, but, as Barabási warns his friends in the social sciences, attempts to formulate a general network of theory of society will likely be frustrated: "The diversity of networks in business and the economy is mind-boggling. There are policy networks, ownership networks, collaboration networks, organizational networks...you name it. It would be impossible to integrate these diverse interactions into a single all-encompassing web."[82] As Barabási recognizes, the astounding complexity of social life renders comprehensive theoretical knowledge of its logics an impossible dream. The computing power that has made contemporary network theory applicable to sociological problems is still no match for it:

> The goal before us is to understand complexity. To achieve that, we must move beyond structure and topology and start focusing on the dynamics that take place along the links. Networks are only the skeleton of complexity, the highways for the various processes that make our world hum. To describe society we must dress the links of the social network with actual dynamical interactions between people."[83]

This study tries to 'dress the links' (a few, anyway) by describing the dynamic interactions that constitute network connections and associations. The rationale for

---

[81] See chapter one for an in-depth discussion of sociological network analysis.

[82] Barabási, Linked: The New Science of Networks, p. 225.

[83] Barabási, Linked: The New Science of Networks, p. 225.

doing so echoes a point that has been made countless times by qualitative methodologists in sociology in their endless quarrels with quantitative colleagues, but it bears repeating here because it is apropos to the topic of sociological network analysis, too. In the study of social life, it really isn't possible to give a satisfying explanation of any concrete happening without telling stories about how people (together, interactively, of course) made it happen. This is how people have been explaining events and actions for thousands of years, and it is a good way. So, my aim in this work has not been to construct a comprehensive chart of the social networks that constitute the biotech industry in San Diego. Instead, this dissertation visits a few places on a roughly sketched map in order to get a feel for the local scenery.[84] It is a report of life on the ground in certain parts of San Diego. The kind of data that makes up the empirical substance of this report is necessarily excised from mathematical network analyses. Those excisions are made in attempts to reduce the complexity of the world of concrete personal experience, which pragmatist philosopher William James called "multitudinous beyond imagination, tangled, muddy, painful, and perplexed."[85] But in order to begin to understand how social networks function, it is necessary to understand how they are folded into this messy reality. 'Corporate interviewing' makes possible this kind of contextualization.

---

[84] The mental map that I've worked from – organized basically as a genealogy of companies on the same family tree – is sketchy, as it must be, but it isn't two-dimensional. It features four dimensions, three representing locations and distances in space, and one representing the passage of time.

[85] William James, "The Present Dilemma in Philosophy," pp. 9-26 in Pragmatism and The Meaning of Truth, Cambridge, MA: Harvard University Press, 1975; pp. 17-18.

The interview data in this research have been supplemented by a wide range of documentary materials – business plans, financial reports, stock offering prospectuses, patents, licenses, legal proceedings, trade publications, scientific literatures, clinical trial reviews, and so on.[86] With information culled from these varied sources, I have assembled professional biographies of Hybritech's scientific entrepreneurs and case histories of companies that they have founded. These have been blended into an historical narrative that recounts the formation of San Diego's biotechnology industry. In doing so, I've tried to emulate business historian Leslie Hannah's preference for "telling history as it is rather than trying to generalise and fit entrepreneurs to the rather inadequate economic theories that we have."[87] Of course, the idea that history can be told 'as it is' is problematic. History told is always history interpreted. Still, I believe that many historians and social scientists harbor misconceptions about the relationships between 'theory' and 'history as it is.' I cannot address the problem here other than to assert that, while historical accounts cannot be 'concept free,' neither can social science fully explicate its conceptual frameworks and grounds of inference.

---

[86] This work touches on a wide variety of technical subjects. For general background information in these areas, and. in particular, fundamental facts and explanations typically taken for granted as common knowledge in scientific literatures, I have relied on Neil A. Campbell, Biology, 4th ed. Menlo Park, CA: Addison-Wesley, 1996; Pauline M. Doran, Bioprocess Engineering Principles, San Diego, CA: Academic Press, 1995; Kenneth Lange, Mathematical and Statistical Methods for Genetic Analysis, New York: Springer, 1997; Harvey Lodish, David Baltimore, Arnold Berk, S. Lawrence Zipursky, Paul Matsudaira, and James Darnell, Molecular Cell Biology, 3rd ed., New York: Scientific American Books, 1995; Robert A. Myers, ed., Molecular Biology and Biotechnology, New York: VCH Publishers, 1995; William E. Paul, Fundamental Immunology, 4th ed., Philadelphia, PA: Lippincott-Raven, 1999; Hooman H. Rashidi and Lukas K. Buehler, Bioinformatics Basics, Boca Raton, FL: CRC Press, 2000; Lubert Stryker, Biochemistry, 4th ed., New York: W.H. Freeman & Co., 1995; Geoffrey L. Zubay, Biochemistry, 4th ed., Reading, MA: Addison Wesley, 1998.

[87] Leslie Hannah, "The Entrepreneur in History," pp. 31-42 in Prime Mover of Progress: The Entrepreneur in Capitalism and Socialism, ed. Israel Kirzner, London: The Institute of Economic Affairs, 1980; p. 34.

And because it can't, neither can it formulate any coherent methodological or epistemological distinction for the bodies of knowledge that its practitioners generate. Certainly, when disciplinarians of various stripes tell stories about what happened in the past, sociological histories will differ from psychological histories, economic histories, or natural histories. And those belonging to different schools of thought within disciplines will tell different stories, too. But no set of theoretical or conceptual presuppositions affords any sort of epistemological privilege or distinction. Accounts of all kinds – abstract or concrete, explanatory or descriptive, nomothetic or idiographic, 'disciplined' or 'undisciplined' – rest, at last, on their plausibility.

This historical account of San Diego's biotechnology industry is a 'realist tale,' as ethnographer John van Maanen calls stories that relate events and happenings in a simple narrative form.[88] It is a 'realist tale' that aims to be 'objective,' not in the sense that it represents the only 'correct' interpretation of what has transpired in San Diego's biomedical community in the last twenty years, but rather because it hews closely to the 'data,' to the stories that entrepreneurs and scientists tell about their own activities. From these many varied perspectives on the facts, I have extracted an account that does not privilege any particular view, yet tries to tell the story in a way that the participants themselves can recognize as faithful to their own experiences. It places facts and interpretations of facts in cultural and historical context. The facts in the story are facts of this sort: there was, in the city of San Diego, a company called

---

[88] John van Maanen, Tales of the Field: On Writing Ethnography, Chicago: University of Chicago Press, 1988. Van Maanen is fully aware of the epistemological baggage that realism carries around with it. He uses the term with a touch of irony. Realist tales are about things that really happened, but they're tales nonetheless.

Hybritech. The company rented space, raised money, hired and fired people, developed and marketed products, reported profits and losses, and engaged in a host of other activities. There are broad agreements among participants and onlookers regarding many facts of this kind. But this doesn't mean that there is a definitive story to be told about them. Just how and why these things happened as they did, and what it all meant, are necessarily matters of interpretation.

Putting together the full universe of facts about the formation of the San Diego biotechnology industry in a narrative that could pass as definitive would be far too complex a task for any single person, no matter how well situated. Participants in the process, first-hand witnesses to history, can't do this any more than they can stand in two places at once, and those coming on the scene afterwards, journalists or social scientists, for example, can't do it, either, no matter how extensive is the documentation at their disposal. They can never learn the story in its entirety because the whole truth is never known by anyone. It just isn't available. The events that comprise something like the history of a company or the development of an industry are far too complicated for that. There will always remain uncertainties and gaps of knowledge. These are ineliminable, and they make it impossible for historical tales to masquerade as complete or comprehensive. This doesn't mean that no 'true stories' can be told. It simply means that there are many 'true stories' to tell.[89] So, this isn't the last word. It's just a story, just one among many, just another. But it's based on a

[89] This assumes that it may be possible to distinguish between 'true' and 'false' stories with reasonable degrees of moral certainty.

fair bit of research, and a pretty thorough familiarity with the facts and events in question.

Beyond this, there is another kind of understanding to be culled from a realist presentation of this kind. As personal testimonies, the views expressed in the interviews on which the story is largely based represent interpretations and opinions. But even if these bits of anecdotal evidence are flawed, even if recollections are biased and inaccurate, and even if accounts offered by different participants are sometimes contradictory, from them much can be learned about the kinds of places that Hybritech and its progeny were and are, and how these companies and individuals within them have gone about pursuing their objectives. The reason is this: the testimonies of witnesses, whether true, false, or somewhere in between, naturally draw on particularized cultural repertoires for describing events and actions. These are established ways of understanding and talking about motives and practices that are specific to the 'social worlds' of the life sciences, the pharmaceutical industry, and others that have become intermingled in the field of commercial biotechnology. Statements framed in these vocabularies express attitudes and cognitive and moral orientations that have characterized these various social settings, and the new 'hybrid' forms of life found in the biotech industry, as well.[90] Knowledge of these conventions of communication and interpretation (and action) cannot be found in facts and figures reported in industry databases, government documents, and the like – the sources of

[90] For elaborations of this methodological claim, see H.M. Collins, "The Meaning of Lies: Accounts of Action and Participatory Research," pp. 69-76 in Accounts and Action, eds. G. Nigel Gilbert and Peter Abell, Aldershot: Gower, 1983; and C. Wright Mills, "Situated Actions and Vocabularies of Motive," American Sociological Review 5, 1940: 904-913.

information upon which sociological and economic studies of biotechnology typically rely.[91]

WHY HYBRITECH?

To sum up, this report is a true story about an historical process, the creation of a new social space, and the construction of a web of social networks featuring innumerable interactions and associations. It is also, simultaneously, an interpretive account, based on historical facts, of the formation of a new 'hybrid culture.' One interview subject, on listening to a description of this project, commented that I was "telling the wrong story." From his point of view, any account of local developments in this field must begin with technologies that were developed at the city's academic research institutions. I have no quarrel with the suggestion that scientific work conducted at UCSD, Scripps, and Salk has been a crucial element in the formation and continued growth of the San Diego biotechnology industry. From this angle, a perfectly legitimate account can be constructed.[92] It is not my intention to overplay the importance of Hybritech or its success for later happenings. The histories of many other companies and organizations in the city are noteworthy, too, although, in this work, some of them are mentioned only in passing. Neither do I want to exaggerate the place in the story of Hybritech's founders or its scientific and managerial teams. Many other people whose stories are not told here made crucial contributions to the

[91] Obviously, to learn from others in this way, one must be open to the idea that there may be something valid in descriptions that actors provide of their own activities and those of others. (And, of course, it is not necessary to accept uncritically all that one is told).

[92] And some have been – see, for example, Carolyn Lee and Mary Walshok, "Making Connections: The Evolution of Links Between UCSD Researchers and San Diego's Biotech Industry," UCSD Connect, March 2000; Mary L. Walshok, Edward Furtek, Carolyn W.B. Lee, and Patrick H. Windham, "Building Regional Capacity: The San Diego Experience," Industry & Higher Education February 2002: 27-42.

development of biotechnologies in San Diego. I don't intend to slight them. Still, the Hybritech people were on the scene first, and the early successes and the subsequent sale of the company to Eli Lilly were pivotal events, not only for San Diego, but for the biotechnology industry at large. And when the company was sold, many at Hybritech went on to start other firms nearby. Many did it more than once. They were also among the first industry people in San Diego to become serial entrepreneurs. This is why I'm telling their stories.

The Hybritech alumni don't need anyone to defend the historical significance of their efforts. Some toot their own horns loudly, and readily claim the credit that they believe they deserve. It's hard to fault them for it.[93] Without any special shows of modesty, they can simply point to all of the successful companies that they and their colleagues have founded in the city. As of August 1999, four of the five largest biotech firms in San Diego were founded by former Hybritech executives and scientists.[94] Howard Birndorf says: "The initial Hybritech folks were true enterpreneurs who did it again and again. Dozens of companies came from Hybritech. We are one of the reasons the San Diego industry has flourished."[95] Birndorf is

---

[93] The tooting is more than bald personal aggrandizement or self-centered scorekeeping, although it may often be interpreted as such. Many of my interview subjects were curious to know to whom else I had talked or intended to talk. Perhaps they asked in order to find out if I knew what I was doing, to learn what I might have heard about them, or to make helpful suggestions about other informants (as many did). One subject, after making the inquiry and hearing some of the names on my list of people to interview, remarked: "Oh, all the big egos." I suppose it's true that there are big egos among this bunch of successful entrepreneurs, but, as I indicate in chapters below, these people also have sound instrumental reasons for seeking recognition. In the high-tech culture of San Diego's life science industry, credit for being a good entrepreneur is a scarce and valuable commodity.

[94] Gig Patta, "Book of Lists, 2000: Largest Biotechnology Companies," San Diego Business Journal, December 30, 2000, pp. 86-87.

[95] Quoted in Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, Cambridge, MA: Perseus Publishing, 2000; p. 52.

exactly right. They are one of the reasons. There are plenty of others, too – biotechnology has flourished in San Diego for numerous reasons. Ivor Royston, Birndorf's partner in founding Hybritech, acknowledges this and provides a short list. He contends that the "right factors" – the scientific community, entrepreneurs, managers, and the creation of a supporting infrastructure "all came together in harmonic convergence."[96]

Royston's description finds a place for individual and collective actions, for many different groups of people, and also for the play of chance and accident. His analysis is a balanced one, in my opinion. A lot went into the making of San Diego biotechnology, as Royston says, and far more than can be fit into one book, so the story told here is necessarily selective. In order to highlight the social character and substance of bioentrepreneurship, I've chosen to tell the stories of persons belonging to a particular group, not because they did everything by themselves, but precisely because they didn't.[97] I focus on actions taken by these individuals in order to show just how socially distributed is the 'entrepreneurial function' in the world of biotechnology. In telling the Hybritech story, I recount personal contributions because they were important, but also to show that, as crucial as they turned about to be, each was still just a small piece in a very large puzzle.

---

[96] Ivor Royston, "San Diego's Formula for Biotech Success," San Diego Union-Tribune, June 19, 2002.

[97] A virtue of the biographical method, as Robert M. Young points out, is that as it becomes more contextualizing and self-consciously sociological, it can more effectively (and empirically, rather than philosophically) deflate the conceits of individualism. Young remarks: "The more influences represented in a hagiographic biography, the less genius...more articulations mean more social embedding and more ways of holding the Gulliver of human arrogance by Lilliputian ties." Robert M. Young, "Biography: The Basic Discipline for Human Science," Free Associations 11, 1988: 108-130.

II. ENTREPRENEURS, CULTURE, AND TECHNICAL CHANGE

> It is evident that many great and useful objects can be attained in this world only by cooperation.
>
> Thomas Babington Macaulay

HYBRID FORMS OF LIFE

At the northern end of San Diego, in the Sorrento Valley, and on Torrey Pines Mesa, there can be found today dozens of recently constructed industrial complexes and hundreds of newly outfitted pharmaceutical laboratories that apply the latest bioscientific techniques. At these locations, thousands of industrial scientists, supported by billions of dollars in private capital investments, are attempting to develop treatments and cures for human diseases. When big-time biological research arrived in San Diego in the 1960s at the University of California, San Diego, the Scripps Research Institute, and the Salk Institute for Biological Studies, many expected scientific and medical benefits to flow from it, but few could have imagined this outcome. Commercial pharmaceutical research and development had never been a significant component of the region's industrial base. In all of Southern California, only Allergan, Inc., an opthalmic products company headquartered in Irvine, could advertise itself as a major drug developer and manufacturer. Towering financial barriers to market entry and the control of traditional methods of pharmaceutical production by large corporations made the ethical drug trade an unlikely source of new economic growth on the West Coast. As recently as 1980, there was little indication that this situation would soon change dramatically. Yet, in San Diego,

biotechnologies are beginning to pay out unanticipated dividends to regional investments in basic science.[1] How did this circumstance come about?

This dissertation is an attempt to provide some modest answers to this question. It is a social history of how the biotechnology industry began and grew in San Diego in the late 1970s and the early 1980s. It is a tale of how the unexpected happened. In retrospect, that the commercial utilization of new tools fashioned in the biosciences took root in the city of San Diego is no great surprise. What better place could there be for this kind of activity? The research and development programs pursued by biotechnology companies everywhere have been established and sustained through the formation of close ties with bioscientists located in universities and other academic research institutions.[2] It could hardly have been otherwise. In the 1970s, these were the only places in which biotechnologists could be found. It is unlikely that the cluster of science-driven biomedical companies that many now deem vitally important to San Diego's economic future would have appeared without the assistance of the city's technical expertise in residence.[3] Yet, only with the benefits of hindsight

---

[1] See Edward J. Blakely and Kelvin W. Willoughby, "Choosing a Strategy for Local Industry Development from Biotechnology," Working Paper #520, Biotechnology Industry Research Group, University of California at Berkeley.

[2] See Martin Kenney, Biotechnology: The University-Industry Complex, New Haven, CT: Yale University Press, 1986; Lynne G. Zucker, "Intellectual Capital and the Birth of U.S. Biotechnology Enterprises," Working Paper #4653, National Bureau of Economic Research, Cambridge, MA, 1994; Lynne G. Zucker and Michael R. Darby, "Virtuous Circles of Productivity: Star Bioscientists and the Institutional Transformation of Industry," Working Paper #5342, National Bureau of Economic Research, Cambridge, MA, 1995.

[3] Of course, decisions concerning the location of new biotechnology companies involve the consideration of a wide range of factors in addition to proximity to the relevant 'knowledge base.' Also impacting the conditions and costs of doing business are the presence of an educated labor force; local wage scales; going rates for real estate and industrial space; city, county, and state taxes and regulations; convenience of access to materials suppliers and financial resources; and the relative 'quality of life' in a region, to name just a few. See Edward J. Blakely, Brian H. Roberts, and Philip

can this participation by academic scientists be taken for granted. Biotechnologies were not originally transferred from their academic cradles to sites of industrial development by any conventional (i.e., formally routinized) means. They were not immediately embraced and adopted by established firms in the pharmaceutical business. The biotechnology industry came into being as a wave of entrepreneurial start-up companies fueled by venture capital, in which university faculty and other academic researchers were often centrally involved as founders, directors, and officers.

Because of their peculiar lineages, biotech start-ups have appeared as novel organizational forms. They merge basic biological research and pharmaceutical product development in unprecedented ways. As Paul Rabinow has emphasized in an anthropological study of Cetus Corporation and its stewardship of Kary Mullis' Nobel Prize winning invention of PCR technology,[4] the business of biotechnology has engendered a dynamic recombination of scientific and commercial cultures, the creation of new knowledge-making and organizational practices. Biological drug discovery and design is an interdisciplinary enterprise. In biopharmaceutical work,

---

Manidis, "Inducing High Tech: Principles of Designing Support Systems for the Formation and Attraction of Advanced Technology Firms," International Journal of Technology Management, 1987, 2, 3/4: 337-356; and Kelvin Willoughby and Edward J. Blakely, "Making Money from Microbes: Finance and the California Biotechnology Industry," Working Paper #89-116, Center for Real Estate and Urban Economics, University of California, Berkeley, 1989. As it happens, San Diego has been deemed suitable by many bioentrepreneurs.

[4] Paul Rabinow, Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press, 1996. Cetus Corporation was a Bay Area company founded in 1971. Initially, it aimed to improve traditional chemical and bioprocessing techniques employed in the pharmaceutical industry. In the mid-seventies, however, Cetus incorporated a recombinant DNA program, to which Mullis was hired, and it later became known as a 'biotech' company when the use of that term became current. PCR stands for polymerase chain reaction. It is the 'exponential amplification' (the artificially accelerated replication) of bits of genetic material that can be used for various purposes. Cetus was purchased in 1991 by Chiron, another Bay Area biotechnology firm that became one of the industry's leading success stories.

molecular biologists and geneticists, biochemists, immunologists, biophysicists, pharmacologists, toxicologists and many others commonly team up on drug development projects. The viability of a biotechnology firm often depends on the extent to which persons with university backgrounds and those with experience in industry are able to work together to manage R&D programs and to coordinate the company's scientific and business functions. Traditional institutional boundaries and economies of work found in universities and the pharmaceutical industry tend to inhibit effective collaborations of this kind. Biotech start-ups are designed to enable them. Research conducted in the labs of small biopharmaceutical companies is typically regulated by some hybrid mixture of academic and industrial rhythms and forms of discipline.[5] In this field, technological innovations have emerged from within the making of organizational innovations.[6] The transformation of biotechnologies from experimental techniques in the life sciences to functional tools

---

[5] In a study of organizations developing monoclonal antibody diagnostics, Michael Mackenzie, Alberto Cambrosio, and Peter Keating found little to distinguish industrial and academic laboratories, at least insofar as technical production and the practical activities of scientific workers within them was concerned. See Mackenzie, Cambrosio, and Keating, "The Commercial Application of a Scientific Discovery: The Case of the Hybridoma Technique," Research Policy, 1988, 17: 155-170. For other accounts of daily life and ecologies of work in biotechnology companies, see, Rabinow's book, Making PCR; Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995, ch. 4.

[6] Large pharmaceutical companies have begun to heed the lesson. Novartis, for example, is attempting to improve and streamline its product development efforts by incorporating genomics and bioinformatics programs. In order to accomplish this technical change of direction, the company is reorganizing. It has hired an academic scientist, Dr. Mark Fishman, former professor at Harvard Medical School and chief of cardiology at Massachusetts General Hospital, to oversee its R&D operations. Fishman has announced that he wants to establish an open, collegial working environment for his corporate scientists: "I've never been in a pharma lab, but I know I don't want stodgy, secretive space." Quoted in Susan Diesenhouse, "A Drug Company's Man in Tweed," New York Times, May 25, 2003.

employed in the manufacture of pharmacological goods has been accomplished through the creation of new economic and scientific spaces.[7]

This deep immersion of life scientists in commerce, while commonplace today, represents a striking departure from the past. But this change did not proceed according to the logic of some grand design. It was not orchestrated by professional managers in the pharmaceutical industry, nor by university administrators or government bureaucrats. The formation of the biotechnology industry was initiated by spontaneous entrepreneurial actions. It came about as small groups of identifiable persons – bioscientists and venture capitalists – began doing things that had not been done before. In a very general sense, the biologists and medical researchers who forayed into commerce were merely mimicking the familiar examples of academic engineers and chemists, groups that have long defined their roles to include participation in industry. Thus, sociologist Sheldon Krimsky was able to say of the entanglement of university-based gene splicers in private biotech ventures: "Molecular biology was not setting any precedents in the relations between academe and industry; it was simply following an established pattern."[8] But these activities were novel – and, for many 'outsiders,' startling – because of the particular scientific disciplines and technologies involved, and because of the specific business forms to which they

---

[7] See Kenneth Green, "Creating Demand for Biotechnology: Shaping Technologies and Markets," pp. 164-184 in Technological Change and Company Strategies: Economic and Sociological Perspectives, eds. Rod Coombs, Paolo Saviotti, and Vivien Walsh, London: Harcourt Brace Jovanovich, 1992; Martin Kenney, "Biotechnology and the Creation of a New Economic Space," pp. 131-143 in Private Science: Biotechnology and the Rise of the Molecular Sciences, ed. Arnold Thackray, Philadelphia, PA: University of Pennsylvania Press, 1998.

[8] Sheldon Krimsky, Genetic Alchemy: The Social History of the Recombinant DNA Controversy, Cambridge, MA: MIT Press, 1982, p. 204.

gave rise, i.e., entrepreneurial start-ups that began, not with products to market or even well-defined manufacturing processes, but only with plans and schedules for R&D operations. These aspects of the biotechnology business followed no established pattern.

When the sources of this kind of innovation and organizational change in economic production are topics of social research, analysts are obliged to acknowledge the roles played by entrepreneurs. In fact, as I will try to show in this study, the activities of entrepreneurs ought to be given priority in causal explanations. As economist Peter Temin maintains: "While all men are created equal in the sight of God and the U.S. Constitution, not all individuals are equally important to the economy."[9] Entrepreneurs, Temin goes on to say, are particularly important for economic growth and change. In his view, they are the sources of innovation and expansion in capitalist economies: "Entrepreneurs see new opportunities, invent new machines, discover new markets. They are change agents, performing a different function from that of the manager, who works within a known technology, organization, and market."[10] In accounting for innovation and change in high-tech fields, it may be possible to identify and weigh the relative importance of various necessary elements – for example, scientific knowledge, financial capital, skilled labor, managerial acumen, workable economic and legal environments, and a host of additional factors. Yet, the presence of some or all of these inputs or conditions, in

---

[9] Peter Temin, "Entrepreneurs and Managers," pp. 339-355 in Favorites of Fortune: Technology, Growth, and Economic Development Since the Industrial Revolution, eds. Patrice Higonnet, David S. Landes, and Henry Rosovsky, Cambridge, MA: Harvard University Press, 1991, p. 339.

[10] Temin, "Entrepreneurs and Managers," p. 344.

any combination, is never sufficient to explain the emergence of new techniques of production or new organizational forms. For such accounts, entrepreneurial creativity is indispensable. In concrete terms, no social change is realized until human beings act to make it so, and in the case of technological and organizational inventions or innovations, none is ever implemented without the catalytic spark that entrepreneurs provide.

In San Diego and other centers of commercial biotechnological development, scientific and entrepreneurial roles have often been combined and played by the same persons. Professors of biology and medicine have acted, not only as inventors, but also as prime movers in the social organization of efforts to apply new life science techniques to the production of health care commodities. As in other locales, the new economic and scientific spaces that constitute the biotechnology industry in San Diego were simultaneously opened up and occupied by small start-up companies 'spun out' of the city's academic research institutions or existing firms by scientific entrepreneurs. The innovative dimensions of this phenomenon are rooted in its mixture of persons, conventions, practices, and bodies of knowledge drawn from different institutional milieux, those of science, finance, and commerce. The phenomenon continues to reproduce itself. San Diego's biomedical research community has become what urban planners and economic geographers call an 'incubator' of innovative high-tech start-ups.[11] Economic policy analysts Edward J. Blakely and Kelvin W. Willoughby observe that:

---

[11] For general discussions of high-tech 'incubation' in a practical vein, see Alistair M. Brett, David V. Gibson, and Raymond W. Smilor, eds., University Spin-Off Companies: Economic Development, Faculty Entrepreneurs, and Technology Transfer, Savage, MD: Rowman and Littlefield, 1991; Arnold

> [T]here is a complex industrial ecology associated with biotechnology. The firms choose to locate neither randomly nor entirely in order to be close to similar firms. Rather, it appears that they emerge in locations that have a nurturing biotechnology milieu. The presence of a critical biotechnology human-resource base creates its own dynamic, which diffuses into the surrounding medical, electronic, and other industries. Thus, what develops is a local biotechnology-generation complex.[12]

There now exists in the northern suburbs of San Diego such an environment. This is an 'entrepreneurial culture' in which the know-how and the human and material resources necessary for capitalizing on scientific and commercial opportunities flow more or less freely.[13] Knowledge and information travel in the local biomedical community through networks of researchers, executives, investors, and individuals associated with numerous organizations providing professional services to developing high-tech enterprises. The distinctive patterns of action that

---

C. Cooper, The Role of Incubator Organizations in the Founding of Growth-Oriented Firms, West Lafayette, IN: Institute for Research in the Behavioral, Economic, and Management Sciences, Krannert Graduate School of Management, Purdue University, 1985; Raymond W. Smilor and Michael Doud Gill, Jr., The New Business Incubator: Linking Talent, Technology, Capital, and Know-How, Lexington, MA: Lexington Books, 1986. Works in this genre typically define high-tech 'incubation' as a function of organizations and institutions. They focus on the development of administrative principles and guidelines for the construction of offices, agencies, and institutional interfaces that will facilitate technology transfers and the formation of new ventures.

[12] Edward J. Blakely and Kelvin W. Willoughby, "Transfer or Generation? Biotechnology and Local-Industry Development," Reprint #244, Institute of Urban and Regional Development, University of California at Berkeley, 1990.

[13] The kind of social space that I am calling an 'entrepreneurial culture,' and that Blakely and Willoughby call a 'local biotechnology-generation complex,' goes by many other names, as well. Observing the ways in which business, science, and engineering are conducted in Silicon Valley, Kenney concludes that the place has become an "entrepreneurial region." See Martin Kenney, ed., Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, Stanford, CA: Stanford University Press, 2000. Analyzing the same terrain, Lee, et al. call Silicon Valley a "habitat" for entrepreneurs. See Chong-Moon Lee, William F. Miller, Marguerite Gong Hancock, and Henry S. Rowen, The Silicon Valley Edge: A Habitat for Innovation and Entrepreneurship, Cambridge: Cambridge University Press, 2001. Other studies and commentaries by social scientists and business and management scholars have characterized sites of high-tech industrial development as entrepreneurial 'environments,' 'ecologies,' and 'milieux,' and innovation 'hubs,' 'infrastructures,' and 'incubators' (this last term is also commonly employed to refer to organizations dedicated to facilitating communication and resource exchanges in localized entrepreneurial 'environments').

constitute this culture have emerged only in the past twenty-five years, seemingly out of nowhere. There were no precedents for them in either the biological sciences or the pharmaceutical industry. The field of commercial biotechnology has taken shape as an orderly recombination of various elements drawn from each of these domains, but the synthesis is original. And while commercial biotechnology shares in its ways of organizing research and development certain family resemblances with other high-tech industries that tend to cluster geographically in emerging 'technoregions,' there are significant discontinuities here as well.[14] As an industrial sector, biotechnology has its own unique history, its own unique problems, and its own unique ways of getting things done. This dissertation specifies whence came the origins of biotechnology in San Diego. It describes in detail the organizational and technical practices that entrepreneurs and bioscientists have fashioned as the field has grown, and that today characterize its innovative hybrid 'forms of life.'

DOING THINGS TOGETHER

In reporting on the formation of this entrepreneurial field in San Diego, I adopt the simple definition of culture proposed by sociologist Howard S. Becker: "doing things together."[15] By emphasizing concerted action, Becker depicts culture as a

---

[14] These include a slew of financial and organizational conventions related to the industry's unusual dependence on university-based science, its unparalleled degree of regulatory oversight, and its lengthy product development cycles. For a broad summary, see U.S. Congress, Office of Technology Assessment, "Factors Affecting Commercialization and Innovation in Biotechnology," ch. 6 in New Developments in Biotechnology: U.S. Investment in Biotechnology – Special Report, OTA-BA-360, Washington, D.C.: U.S. Government Printing Office, July 1988; see also, U.S. Congress, Office of Technology Assessment, "Appendix C: A Comparison of the U.S. Semiconductor Industry and Biotechnology," pp. 531-541 in Commercial Biotechnology: An International Analysis, OTA-BA-218, Washington, D.C.: U.S. Government Printing Office, 1984.

[15] Howard S. Becker, Doing Things Together, Evanston, IL: Northwestern University Press, 1986, ch. 1.

process. People finding themselves in common circumstances, he says, naturally interact and work together to find solutions to common problems of all sorts. They attempt to reach agreements about the character of these problems and about what can and should be done about them. If they are successful, then they have begun, in effect, to organize a common way of life, traditions of knowing and doing that may serve as guides for managing common problems in the future.

Cultures emerge where people, in the course of coordinating plans and actions, generate shared understandings about their immediate circumstances and about the larger world around them. Cultures persist where courses of actions informed by such shared understandings prove useful or pleasing in concrete practice. Mutual accords about what is the case in the world, and what it means in relation to a group's practical concerns, provide individuals with resources for ordering their perceptions and harmonizing their interests, and so, for organizing effective responses to the demands of experience. By virtue of common orientations to found natural and social environments, people are able to establish and sustain personal relationships, assemble and manage collective projects, and find in the otherwise chaotic flux of appearances coherent meanings and values. Relationships and shared conceptions of proper means and ends in life provide a measure of security in the face of uncertainties that would surely overwhelm individuals going it alone. When people can help each other make sense of events and solve emergent problems, they naturally recognize as common goods the ways of life and forms of cooperation that enable them to do so. Culture, then, on this view, is at once a consequence of social processes in which situations are collectively defined, and in which value and communality are generated, and a

necessary precondition for the consistent and more or less methodical organization of action.[16] It consists in "doing things together."

By highlighting processes of social interaction in this way, Becker distinguishes his view of culture from structuralist and semiotic conceptions that once dominated and are still prominent in anthropology, and to a lesser extent, in sociology. The latter have tended to portray cultures as fixed systems of meaning that order social life from without.[17] Becker, by contrast, understands cultures as constituted by protean modes of action. This interpretation is based on the pragmatic assumption that the world is, in fact, characterized by constant change.[18] Starting from the idea that no

---

[16] Becker writes in a 'symbolic interactionist' idiom. This sociological approach treats the use of language as both the medium and substance of culture. For a series of programmatic statements, see Herbert Blumer, Symbolic Interactionism: Perspective and Method, Englewood Cliffs, NJ: Prentice-Hall, 1969. The pronounced phenomenological tenor of this perspective – that is, its emphasis on situated interactions and concrete ways of knowing, doing, and speaking – derives from its substantial conceptual debts to the pragmatist tradition in American philosophy, and especially the philosophy of science and social psychology of George Herbert Mead. See Mead, The Philosophy of the Present, ed. Arthur E. Murphy, Chicago: University of Chicago Press, 1980 [1932]; Mind, Self & Society: From the Standpoint of a Social Behaviorist, ed. Charles W. Morris, Chicago: University of Chicago Press, 1962 [1934]; and The Philosophy of the Act, ed. Charles W. Morris, Chicago: University of Chicago Press, 1938.

[17] Sherry B. Ortner observed of anthropology in the mid-1980s: "...until very recently little effort has been put toward understanding how society and culture themselves are produced and reproduced through human intention and action." See Ortner, "Theory in Anthropology Since the Sixties," Comparative Studies in Society and History, 1984, 16: 126-166. The coming to currency of various 'theories of practice,' however, in both anthropology and sociology, has since blurred the disciplinary boundary between the two fields, at least as far as conceptual differences regarding their common object – culture – is concerned. For a discussion from a sociological angle, see Ann Swidler, "Culture in Action: Symbols and Strategies," American Sociological Review, 1986, 51: 273-286.

[18] The pragmatists' understandings of order and change were premised on epistemological rather than ontological assumptions. They held that knowledge of the world is always derived from experience. Reality is 'emergent.' It consists in what people come to know and believe in the present. Order and change, then, reside in human consciousness or 'fields of awareness.' For this reason, the pragmatists dismissed ontological questions as meaningless. They understood reality as a process – a process of knowing. In this process, order and change can be perceived only when human beings experience the passage of time. To say that something has remained stable is to say that it is now as it once was in the past. But the experience, or the memory, of the past in the present depends on the appearance of emergent events in consciousness. Emergent events are, by definition, unique products of change. If they were not, then people could not identify them as discrete events (i.e., as discrete instances of change against an experiential background of order, or as discrete instances of order against an

two situations are ever identical, Becker asserts: "No set of cultural understandings, then, provides a perfectly applicable solution to any problem people have to solve in the course of their day."[19] Culture is perpetually in-the-making as established ways of managing affairs are adapted to the minor caprices of daily life, and sometimes to more significant disruptions. In response to the vicissitudes of experience, the common understandings that permit people to coordinate their activities are forever being recreated, revised, and amended. Of course, when members of a group have established customary ways of making the world intelligible and doing things within it, they can, with reference to these procedures, identify as routine or typical many of the situations in which they find themselves. Social interactions often display pronounced similarities that are immediately recognizable to persons familiar with the local culture. In such circumstances, no unusual efforts are required to fashion from conventional or habitual modes of action satisfactory adaptations to exigencies presented or constraints imposed by the novel elements of emergent circumstances.[20]

---

experiential background of change). Without the experience of emergent events, people could not distinguish the present from the past (or from the future, for that matter, which also exists only in the present as anticipation). So, apparent uniformities, regularities, and constancies in the world can be known only when human beings experience change – the universe that human beings sense must be a universe in constant flux. For elaborations, see John Dewey, The Quest for Certainty, ed. Jo Ann Boydston, Carbondale, IL: Southern Illinois University Press, 1988 [1929]; G.H. Mead, The Philosophy of the Present, ed. Arthur E. Murphy, Chicago: University of Chicago Press, 1980 [1932], ch. 1-2; and C.S. Peirce, "Uniformity," pp. 218-227 in Philosophical Writings of Peirce, ed. Justus Buchler, New York: Dover, 1955.

[19] Becker, Doing Things Together, p. 19.

[20] Sometimes, of course, established traditions and ways of life become, not only inadequate guides to action, but problematic in themselves. When accustomed means of adjustment prevent solutions to new problems, they must be substantially reworked or perhaps abandoned. Institutions and organizations may, in particular instances, become so riddled by conflicts and contradictions that grounds of concerted action in the future become threatened, and chances for maintaining continuities in practice become uncertain. And sometimes things do fall apart. Collective projects can endure over time only if stresses and strains embedded or generated within them, or imposed by changes in 'external' environments, can be, not necessarily resolved, but at least managed or accommodated. Sociological

Yet, acknowledging these subtle operations implies that cultures are dynamic, not static, and that collective action within them is improvisational in character.

This makes Becker's approach particularly useful for interpreting processes of technical and organizational change. When established routines for conducting everyday business prove unsatisfactory or problematic, people begin to experiment and innovate. In such situations, they naturally draw on settled knowledge of the world, but they do so in order to manufacture new tools for coping with familiar or unexampled troubles as they appear in situations without precedent. When adaptive solutions to problems are discovered in this way, they sometimes constitute, of necessity, more or less radical departures from the past and conventional modes of action. As Becker says: "given new conditions, people invent culture."[21] Persons who invent culture under such conditions can be called entrepreneurs.[22] Among the many sorts of occurrences that give rise to entrepreneurial revisions of established practices are those in which persons searching for solutions to local problems, whether by chance or by purposive design, move beyond the confines of customary procedures and familiar networks of interaction.[23] In such instances, participants are often

---

investigations of business firm adaptation in the 'new economy' generally stress the advantages of 'flexible' organizational forms. Few have focused on the cultural dimensions of problems confronting traditionally organized corporate entities as they attempt to sustain themselves. For a theoretical exegesis of such troubles confronting large, hierarchical corporations in the post-industrial era, see Erica Schoenberger, The Cultural Crisis of the Firm, Cambridge, MA: Blackwell, 1997.

[21] Becker, Doing Things Together, p. 18.

[22] See Becker's comments on "rule creators" and "moral entrepreneurs" in Outsiders: Studies in the Sociology of Deviance, Glencoe, IL: The Free Press, 1963.

[23] Symbolic interactionists often talk about such activities in terms of traffic across 'social worlds.' This genre of analysis was developed by Anselm Strauss in Negotiations, Varieties, Contexts, Processes, and Social Order, San Francisco: Jossey-Bass, 1978. Several of Strauss' students have applied it in investigations of scientific practice. See, for example, Adele E. Clarke and Elihu Gerson,

obliged, if they are to establish grounds for ongoing cooperation, to create new social spaces, and to synthesize new cultural practices within them.

This is exactly what has happened in the case of commercial biotechnology, where scientists, financiers, businesspersons, and others, have come together to establish new kinds of alliances and new organizational forms, to secure new sources of funding for bioscientific research, and to commence work on new diagnostic and therapeutic tools to be employed in the treatment of human diseases. The persons who built this industry, while of course sharing many general understandings about the world, could refer to no blueprint or formula for what they were attempting to do. They had to devise original solutions to their problems and come to practical agreements about how to implement them. These accords represent innovative departures from the past, but also necessary accommodations with the historical legacies of the various communities and spheres of action that have been linked in the industrial development and application of biotechnologies. Becker's conception of culture provides a vocabulary for describing the entrepreneurial actions that produced these linkages in ways that remain attentive to their immersion in definite social contexts.

As a general theory of action, Becker's approach is vague and imprecise – and appropriately so. The things that people do together are remarkably varied. Social

---

"Symbolic Interactionism in Social Studies of Science," pp. 179-214 in Symbolic Interactionism and Cultural Studies, ed. Howard S. Becker and Michael W. McCall, Chicago: University of Chicago Press, 1990; and Elihu Gerson, "Scientific Work and Social Worlds," Knowledge: Creation, Diffusion, and Utilization, 1983, 4, 3: 357-377. Clarke has also promoted 'social worlds' talk as an alternative to various 'mainstream' organizational theories in sociology. See Clarke, "Social Worlds/Arenas Theory as Organizational Theory," p. 119-158 in Social Organization and Social Processes: Essays in Honor of Anselm L. Strauss. ed. David R. Maines. New York: Aldine de Gruyter, 1991.

and cultural processes unfold kaleidoscopically in their natural settings in different times and places, and this is true whether the result is the reproduction of existing social structures or the innovative assembly of new ones.[24] Becker's interpretive scheme encourages empirical attention to the situated interactions that constitute these processes and comprise the substance of culture-in-the-making. In this work, I employ Becker's definition of culture as a practical heuristic for interpreting the concrete actions and events that have shaped the emergence of commercial biotechnological development in San Diego. My objective is to produce a distinctly sociological account of the 'industrial ecology,' the 'biotechnology-generation complex,' the 'nurturing biotechnological milieu' that has taken up residence in the city. I aim to document the means that participants in this setting have established for doing business and doing science together, and the ways in which these methods sustain the commercial development of biotechnologies.

I believe that this is a useful approach for getting to grips with the dynamics of post-industrial enterprise. In post-industrial economies, information and modes of processing and applying it are salient commodities, currencies of exchange, and factors of production. Progress in such economies derives from the circulation of knowledge and skill rather than brute manufacturing power. The making of technological innovations in post-industrial settings is, as Daniel Bell described it, "a

---

[24] The creativity involved in maintaining established relations and practices ought not to be overlooked. The management or enactment of routines can never be purely formulaic. As Donald Schön remarks: "There is no sure way of learning from past experience." See Schön, "The Fear of Innovation," pp. 290-302 in Science in Context: Readings in the Sociology of Science, eds. Barry Barnes and David Edge, Milton Keynes: Open University Press, 1982; p. 295. Organizational innovations are usually adopted when established habits or conventions start causing more trouble than they are worth. Context, not creativity, distinguishes innovative and routine actions.

game between persons."[25] Yet, many social scientific inquiries into the workings of post-industrial economies yield bloodless accounts that are not about persons at all. They talk about capital, markets, firms, institutions, technologies, and so on, 'doing things.' This dissertation, by contrast, is about knowledgeable, skillful, and informed post-industrial persons, their circumstances, and their collective projects. It is about the people who set the San Diego biotechnology industry into motion, and how they did it. Below I elaborate a range of sociological concepts that can be used to interpret various aspects of scientific entrepreneurship, but Becker's definition of culture nicely sums up how bioscientists and other actors have created and sustained a 'nurturing biotechnology milieu' in San Diego: by 'doing things together.' The business of starting and running new biotechnology firms is fundamentally a social practice, 'a game between persons.'

THE BIG PICTURE OF BIOTECHNOLOGY: A REVIEW OF LITERATURES

Increasingly in the post-war era, social scientists have come to recognize that innovation in high technology is a key to economic competitiveness and the wealth of

---

[25] Daniel Bell, The Coming of Post-Industrial Society: A Venture in Social Forecasting, New York: Basic Books, 1976 [1973], p. 30. Bell referred specifically to situations "in which each person's course of action is necessarily shaped by the reciprocal judgments of the others' intentions." He went on to predict that attempts to 'rationalize' practical decision-making in such situations (via "intellectual technologies" like game theory or systems analysis) would become a distinguishing feature of post-industrial social life. This forecast was off the mark. High-tech innovation is, to be sure, "a game between persons," but not one that has become 'rationalized.' As an anonymous writer for The Economist points out, the process of post-industrial development is far too complex for it: "[T]he replacement of capital with knowledge as a company's most valuable resource is forcing top managers to rethink their jobs. The trouble with knowledge is that it is so much more difficult to manage than capital: fixed in the heads of pesky employees, rather than stored in the bank, and infuriatingly volatile and short-lived to boot. If your boss has a harried and hunted look as he travels the world pressing flesh and puffing egos, it may be because he is trying to do an impossible job." See "The Changing Nature of Leadership," The Economist, June 10, 1995, p. 57.

nations,[26] a vehicle for the social expansion of capital and new modes of production,[27] and a force that can transform culture and political economy on a global scale.[28] No social scientific speculation on the future, optimistic or otherwise, fails to assign to progress in high technology a central role. Whether working toward the end of facilitating, regulating, or simply understanding it, many analysts are now investigating high-tech innovation. And since the early 1980s, students of industrial organization have focused intensively on the workings of the biotechnology industry. Although small, the biotech sector has received special scrutiny because, as an arena of economic and technological enterprise, it is a paradigmatic example of post-industrial development. It is a knowledge-intensive field characterized by new institutional relationships and channels of communication and exchange. While unique in many ways, the biotech industry, like other high-tech fields, is comprised mainly of regional clusters of small, interdependent start-ups. Unlike traditional 'vertically integrated' corporations that seek to assemble and organize operational

---

[26] See, for example, Daniele Archibugi and Jonathan Michie, eds., Technology, Globalisation, and Economic Performance, Cambridge: Cambridge University Press, 1997; Christopher Freeman, Margaret Sharp, and William Walker, eds., Technology and the Future of Europe: Global Competition and the Environment in the 1990s, London: Pinter, 1991; Ralph Landau and Nathan Rosenberg, eds., The Positive Sum Strategy: Harnessing Technology for Economic Growth, Washington, D.C.: National Academy Press, 1986; Nathan Rosenberg, Ralph Landau, and David C. Mowery, eds., Technology and the Wealth of Nations, Stanford, CA: Stanford University Press, 1992.

[27] David F. Noble, America By Design: Science, Technology, and the Rise of Corporate Capitalism, Oxford: Oxford University Press, 1977; and Forces of Production: A Social History of Industrial Automation, New York, Knopf, 1984; Allen J. Scott and Michael Storper, eds., Production, Work, Territory: The Geographical Anatomy of Industrial Capitalism, Boston: Allen & Unwin, 1986; Harley Shaiken Work Transformed: Automation and Labor in the Computer Age, New York: Holt, Rinehart, and Winston, 1984; Michael J. Storper and Richard Walker, The Capitalist Imperative: Territory, Technology, and Industrial Growth, Oxford: Basil Blackwell, 1989; Shoshana Zuboff, In the Age of the Smart Machine: The Future of Work and Power, New York: Basic Books, 1988.

[28] David Harvey, The Condition of Postmodernity: An Enquiry into the Origins of Cultural Change, Cambridge, MA: Basil Blackwell, 1989; Allen J. Scott, Regions and the World Economy: The Coming Shape of Global Production, Competition, and Political Order, Oxford: Oxford University Press, 1998.

resources and tasks internally in hierarchical structures, these companies feature 'flexible' systems of production.[29] They maintain extensive 'horizontal' relations of exchange and cooperation with external entities.[30]

Most biotech companies are basically R&D operations. They are established and sustained through the acquisition or enlistment of capital and specialized know-how and skill. They secure these resources by making connections and entering into collaborations with venture capitalists, corporate partners, universities, research institutions, and often with each other as well. These connections and collaborations are exploited in order to fund research, bolster internal technical and managerial competencies, and access additional resources and forms of expertise that are too costly to develop in-house.[31] In biotechnology, the sources of innovation are

---

[29] Michael J. Piore and Charles F. Sabel, The Second Industrial Divide: Possibilities for Prosperity, New York: Basic Books, 1984; Walter W. Powell, "Neither Market Nor Hierarchy: Network Forms of Organization," pp. 295-336 in Research in Organizational Behavior, vol. 12, eds. L.L. Cummings and B. Shaw, Greenwich, CT: JAI Press, 1990; Charles F. Sabel, "Flexible Specialisation and the Re-Emergence of Regional Economies," pp. 17-70 in Reversing Industrial Decline? Industrial Structure and Policy in Britain and Her Competitors, eds., Paul Hirst and Jonathan Zeitlin, London: Berg, 1989; and "Moebius-Strip Organizations and Open Labor Markets," pp. 23-54 in Social Theory for a Changing Society, eds., Pierre Bourdieu and James S. Coleman, Boulder, CO: Westview Press, 1991; AnnaLee Saxenian, Regional Advantage: Culture and Competition in Silicon Valley and Route 128, Cambridge, MA: Harvard University Press, 1994.

[30] Stephen R. Barley, John Freeman, and Ralph C. Hybels, "Strategic Alliances in Commercial Biotechnology," pp. 311-347 in Networks and Organizations: Structure, Form, and Action, eds., Nitin Nohria and Robert G. Eccles, Boston: Harvard Business School Press, 1992; Gary P. Pisano, Innovation Through Markets, Hierarchies, and Joint Ventures: Technology Strategy and Collaborative Arrangements in the Biotechnology Industry, Ph.D. Dissertation, University of California, Berkeley, 1989; Walter W. Powell and Peter Brantley, "Competitive Cooperation in Biotechnology: Learning Through Networks?" pp. 366-394 in Networks and Organizations: Structure, Form, and Action. eds. Nitin Nohria and Robert G. Eccles. Boston: Harvard Business School Press, 1992.

[31] James E. Gail, "Strategic Alliances as 'Virtual Integration': A Longitudinal Study of Biotech Industry-Level Learning," Academy of Management Journal, Best Paper Proceedings, 1995: 469-473; Julia Porter Liebeskind, et al., "Social Networks, Learning, and Flexibility: Sourcing Scientific Knowledge in New Biotechnology Firms," Organization Science, 1996, 7, 4: 428-433; Walter W. Powell, Kenneth W. Koput, and Laurel Smith-Doerr, "Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology." Administrative Science Quarterly, 1996, 41: 116-145; Weijan Shan, Gordon Walker, and Bruce Kogut, "Interfirm Cooperation and Startup Innovation in the Biotechnology Industry," Strategic Management Journal, 1994, 15: 387-394.

distributed across a range of institutions and organizations. For small companies operating in this field, survival depends on effective networking and the propinquity of suppliers and partners. Biotechnology firms thrive on what economists call 'agglomeration externalities,' benefits that accrue from the concentration of resources in circumscribed geographic settings.[32] According to many analysts, industrial ecologies composed of clustering biotech start-ups generate their own momentum by cultivating or drawing venturers to take advantage of opportunities for innovation and profit thrown up by biological research. Blakely and Willoughby, for example, assert that "this synergistic development continues to attract and develop new biotechnology entrepreneurs, who act as the seed bed of the local economic environment."[33] This is fine as far as it goes, but it doesn't account for the formation of industrial ecologies in biotechnology or tell very much about what exactly it is that bioentrepreneurs do.

To date, most social scientists attempting to explain the emergence of commercial biotechnology in its distinctive forms have adopted 'neo-Schumpeterian' or 'evolutionary' interpretations of technological and organizational innovation.[34]

---

[32] Paul A. David and Joshua Rosenbloom, "Marshallian Factor Market Externalities and the Dynamics of Industrial Location," Journal of Urban Economics, 1990, 28: 349-370; Amy K. Glasmeier, "Factors Governing the Development of High-Tech Industry Agglomerations: A Tale of Three Cities," Regional Studies, 1988, 22: 287-301; Zvi Griliches, "The Search for R&D Spillovers," Scandinavian Journal of Economics, 1992, 94 (suppl.): 29-47; Lynne G. Zucker, Michael R. Darby, and Jeff Armstrong, "Intellectual Capital and the Firm: The Technology of Geographically Localized Knowledge Spillovers," Working Paper No. 4946, Cambridge, MA: National Bureau of Economic Research, 1994.

[33] Edward J. Blakely and Kelvin W. Willoughby, "Choosing a Strategy for Local Industry Development From Biotechnology: Transfer or Incubate?" Working Paper #520, Biotechnology Industry Research Group, University of California at Berkeley, May 1990, p. 33.

[34] See, for example, Steven W. Collins, "Genes, Markets, and the State: The Emergence of Commercial Biotechnology in the United States and Japan," Ph.D. dissertation, University of Virginia, 1994; Martin Kenney, "Schumpeterian Innovation and Entrepreneurs in Capitalism: A Case Study of the U.S. Biotechnology Industry," Research Policy, 1986, 15, 1: 21-31; Luigi Orsenigo, The Emergence of Biotechnology: Institutions and Markets in Industrial Innovation, New York: St. Martin's Press, 1989.

These explanations lean heavily on putative logics of science and finance, or on principles of economic selection that operate in institutional environments or social systems made up of firms, populations of firms, concentrations of capital, labor markets, consumer demands for health care products and services, trade associations, scientific disciplines, universities, government agencies that fund, regulate, and plan, and so on. Analyses framed in these terms typically downplay the significance of individual initiative and action. They are presented as 'tough-minded' assessments of economic, political, and social structural conditions, market processes, and institutional and organizational relations and trajectories. They have little use for 'popular myths' that portray entrepreneurs as heroic risk bearers or mavericks imposing their wills on the world.[35]

The roles of entrepreneurs in the beginnings of the biotech field, then, while regularly noted, have scarcely been treated in any depth. Academic venturers and their financial partners have often been portrayed as agents of social change who engineered novel technological and organizational innovations. Yet, at the same time, it is typically assumed that they did so entirely within windows of opportunity opened by the inexorable workings of science and the capitalist system, or by the fortuitous convergence of biological inquiry and the marketplace within the prevailing

---

[35] It is not clear who actually believes such myths, but it is not uncommon for pundits to assume that they are widely accepted. Philosopher Robert C. Solomon, for example, asserts that entrepreneurship is treated in "typically celebratory but often blithering terms in recent business and popular literature," that in stifling modern corporate environments "the ideal of the entrepreneur appears as an antidote, an alternative, even a savior," and that for individuals mired in such settings, the idea of working for oneself is attractive because it promises a "fantasized form of psychic compensation." See Robert C. Solomon, "Marketing Heidegger: Entrepreneurship and Corporate Practices," Inquiry, 1995, 38, 1-2: 75-81. There is surely truth in these observations, but the blanketing scope of Solomon's imputations is striking.

institutional, economic, and political environments of the 1970s. In a marvelously thorough and widely acclaimed report on the emergence of commercial biotechnology, Martin Kenney has crafted an account of this kind, a story of institutional change that mixes historical description with implicit and diluted forms of technological determinism and economic reductionism.[36] On Kenney's view, the biotechnology industry emerged when "the basic science of biology at a certain historical moment had matured sufficiently to be transferred from the university and transformed into a force of production."[37] He proposes further that the growth of the industry was due to "the recognition by investors that biotechnology could well disrupt old markets, create new products, and cheapen current manufacturing processes."[38] Accordingly, his work describes "the creation of new social relationships to accommodate biotechnology."[39] Here – on a literal interpretation, at any rate – technological discontinuities, and not persons, are identified as the driving forces behind economic and organizational change. The role of the entrepreneur is reduced to discovering before others and effectively taking advantage of objective opportunities generated by scientific progress.

Kenney's story is one, at last, of scientific and economic rationalities coming together to colonize new domains of social life, to transform the norms of the academy

---

[36] Martin Kenney, Biotechnology: The University-Industrial Complex, New Haven, CT: Yale University Press, 1986. Kenney's book is generally recognized as the definitive statement on the birth of the biotech industry. It is hard to find an economic or sociological analysis of the biotech phenomenon that does not refer to it.

[37] Kenney, Biotechnology, p. 240.

[38] Kenney, Biotechnology, p. 132.

[39] Kenney, Biotechnology, p. 4.

and to install new organizational and technical practices in industry. In this tale, biotech entrepreneurs are depicted as economic opportunists, as profit seekers naturally rising to the occasion of new technologies creating new markets, effortlessly identifying the possibilities for personal gain that have appeared as a result.[40] Kenney assumes that economic opportunities created by biotechnologies were transparently clear to actors on the scene in the 1970s, that bioscientific advances had obviously opened up new markets for entrepreneurs to exploit, and that subsequent organizational transformations in the academy and pharmaceutical product development followed directly from technological innovations fashioned within the capitalist system of production and exchange. He acknowledges that entrepreneurship was a necessary element in the commercialization of biotechnologies, but also portrays it, in a sense, as epiphenomenal. There is, however, a subtext that surfaces occasionally within Kenney's narrative to suggest a very different interpretation. Discussing the formation of the biotech sector in the health care industry, the new commercial roles for life scientists occasioned by this happening, and ensuing transformations in university-industry relations that accelerated during the late 1970s and early 1980s, Kenney states:

> The history of consulting in molecular biology and allied fields is short; this was merely another "basic" science before 1976. In less than a decade, however, a new industry and a new labor force have been created, and at the center of this maelstrom of activity were "pure"

[40] Says Kenney, in Biotechnology, p. 91: "In a society based on achieving high salaries and a good life style, these professors' decisions to participate in the commercialization of their science is only to be expected." Kenney cites additional personal characteristics and motivations that may spur bioentrepreneurs (pp. 97-98), including "competitiveness," "satisfaction in moving downstream from research to development," and "the ennui that sets in for some professors," a condition for which "the thrill of operating a small, growing company" can serve as a tonic. He does not, however, pursue these themes. Exactly how they fit, if at all, into his larger 'neo-Schumpeterian' explanatory framework is never made clear.

> scientists – molecular biologists. The creation of this new labor force is the story not of sweaty factory workers but of "think workers" dressed in laboratory coats. And, conversely, it is a story of capitalists, though not necessarily in Brooks Brothers suits; many are still in lab coats. The arrangements described in the previous chapter [formal university-industry partnerships] were in actuality a consequence of and a reaction to the activities of these entrepreneurial professors.[41]

So, which is it, then? Are these phenomena adequately accounted for by the dynamics of 'science' and 'capitalism,' or would it be more accurate to attribute them to the "activities of these entrepreneurial professors?" Is the appropriate 'level of analysis' for studying the emergence of the biotech industry that of abstract logics working in the sciences and the capitalist system of exchange or that of particular events and actions? Were the commercialization of biotechnologies and the formation of entrepreneurial ventures for this purpose preordained, called out by forces emanating from within the laboratory, the marketplace, and relevant institutional environments? Following the invention of biotechnologies within the particular cultural, scientific, and economic conditions that characterized the late 1970s, was it inevitable that entrepreneurs would appear to promote them? Or were spontaneous entrepreneurial actions themselves the original catalysts for the social changes that have appeared in the wake of biotechnologies and biotechnologists wherever they have traveled in the world? Kenney provides generalized descriptions of boundary-spanning social ties that connect universities and scientific disciplines with venture capital firms, start-up companies, large corporations, and so on, associations that have come to constitute the field of biotechnology.[42] But generalized descriptions of

---

[41] Kenney, Biotechnology, p. 91; emphasis added.

[42] Kenney, Biotechnology, ch. 5-8.

patterns of social interaction can be formulated only after interactions have become conventional. Kenney spares but a few pages to relate the specific situated actions of entrepreneurs who initiated these sorts of connections.

The logical tension present in Kenney's explanatory framework does not reflect the complexity of its empirical object, or what economists, management scholars, and social scientists often describe as the 'elusive' character of entrepreneurship.[43] Rather, the sources of this paradox reside in theoretical assumptions that Kenney borrows from Joseph Schumpeter. Kenney's account draws on Schumpeter's general theory of capitalism, incorporating its postulation of economic "statics" and "dynamics."[44] Schumpeter considered technological innovation an important source of economic change, and believed that standard economic approaches were unable to account adequately for its role. But Schumpeter located the link between 'static' and 'dynamic' moments of the economic process in the figure of the entrepreneur – an extraordinary individual who disrupts an economy in equilibrium by extraordinary means.[45] Kenney does not follow Schumpeter down

---

[43] Periodic reviews of entrepreneurship studies often lament the chronic conceptual disunity that characterizes the field, but invariably chalk it up, as do Raphael Amit, Lawrence Glosten, and Eitan Muller, to "the interdisciplinary character of entrepreneurship." See Amit, Glosten, and Muller, "Challenges to Theory Development in Entrepreneurship Research," Journal of Management Studies, 1993, 5: 815-834. Deborah Brazeal makes similar observations in "The Genesis of Entrepreneurship," Entrepreneurship: Theory & Practice, 1999, 23: 29-45. I discuss theories of entrepreneurship in greater detail below, in chapter two.

[44] Joseph A. Schumpeter, The Theory of Economic Development: An Inquiry into Profits, Capital, Credit, Interest, and the Business Cycle, trans. Redvers Opie, New Brunswick, NJ: Transaction Books, 1983 [1926].

[45] Kenney subscribes only to Schumpeter's early analysis of entrepreneurship that envisioned organizers of new ventures unleashing "gales of creative destruction," rushing to fill new economic spaces and displacing established firms through the implementation of innovative means of production that render conventional competencies obsolete (see Joseph A. Schumpeter, The Theory of Economic Development, 1983 [1926]). He presents the biotech industry as a refutation of Schumpeter's later

this interpretive path. He does not tell tales of leadership or charisma. Where Schumpeter depicted the personal motives and qualities of entrepreneurs as the animating breath of life in processes of economic change,[46] Kenney talks about market potentials created by new technologies, and the strategic gambits of individuals and firms moving to exploit them. At the level of individual action, Kenney finds only rational calculation.[47] Kenney's reliance on Schumpeter's analytical categories – without adhering faithfully to Schumpeter's conception of entrepreneurship and the

---

thesis which postulated that corporate bureaucracies had, through expansion and the internal development of technical power, wrested control of the innovation process from individual entrepreneurs, erecting insurmountable barriers to market entry, and paving the way for a de facto socialist future. See Joseph A. Schumpeter, Capitalism, Socialism, and Democracy, New York: Harper, 1942. Kenney's discussion of this later work is found in "Schumpeterian Innovation and Entrepreneurs in Capitalism: A Case Study of the U.S. Biotechnology Industry," Research Policy, 1986, 15: 21-31. Others lately reevaluating the notion that biotechnologies have significantly expanded existing markets or created new ones note the sluggish movement of bioengineered products through development pipelines and across regulatory hurdles, and speculate that the economic and social structural impacts of products manufactured by small firms may be relatively minor. See, for example, Frederick H. Buttel, "How Epoch Making are High Technologies? The Case of Biotechnology," Sociological Forum, 1989, 4, 2: 247-261; and Robert Teitelman, The Profits of Science: The American Marriage of Business and Technology, New York: Basic Books, 1994, ch. 10.

[46] Joseph A. Schumpeter, Essays: On Entrepreneurs, Innovations, Business Cycles, and the Evolution of Capitalism, ed. Richard V. Clemence, New Brunswick, NJ: Transaction, 1989; see, especially, ch. 3, "The Instability of Capitalism"; ch. 18, "The Creative Response in Economic History"; and ch. 21, "Economic Theory and Entrepreneurial History." See, also, Joseph A. Schumpeter, The Theory of Economic Development: An Inquiry into Profits, Capital, Credit, Interest, and the Business Cycle, trans. Redvers Opie, New Brunswick, NJ: Transaction Books, 1983 [1926].

[47] Apparently, for Kenney, personalities and individual motives and talents are significant only to the extent that they influence decisions to make such calculations and then to act in determined, methodical ways when clear paths to profit are indicated. Elsewhere, he refers to entrepreneurial "dedication" and "vision," but also describes entrepreneurship, following Schumpeter, as an expected response to certain material conditions, a capacity to recognize objective opportunities: "The market potential created by new technologies and possible new products encourages a rush of entrepreneurs into what Schumpeter termed a 'New Economic Space.'" See Martin Kenney, "Schumpeterian Innovation and Entrepreneurs in Capitalism: A Case Study of the U.S. Biotechnology Industry," Research Policy, 1986, 15: 21-31; quote on p. 23.

'nonrational' sources of innovation – prevents him from coherently integrating particular actions and events into his causal explanations of larger social processes.[48]

There is much to be learned from Kenney's report. It documents the structural and institutional preconditions of commercial biotechnology, the playing field on which scientific entrepreneurs formulated and carried out plans in order to accomplish their ends, and it traces the broad contours of the social and economic changes that have appeared through the creation of this industry. But Kenney's account of entrepreneurship is inadequate. In fact, his story is hardly about entrepreneurship at all. As a professed Schumpeterian, Kenney credits scientific entrepreneurs with playing important roles, but he has little to say about the actual work that they have done. He describes the consequences of entrepreneurial actions, but neglects the entrepreneurial process itself. This omission inadvertently slights the creativity and the contributions of the persons who built the biotech industry from the ground up. Worse, it ultimately undoes many of the substantive conclusions that Kenney draws about systemic and institutional sources of innovation said to have induced and sustained efforts to commercialize biotechnologies. Kenney provides a masterful sketch of the structural transformations wrought by biotechnologies during the first decade of their careers in business, but he misrepresents the relationships between

[48] Here, I do not mean to endorse Schumpeter's general theory of capitalism. Many critics have cited logical inconsistencies in Schumpeter's uneasy marriage of economic 'statics' and 'dynamics,' and in his dual methodological commitments to economic modeling and economic history as means of accounting for them. See, for example, Harry F. Dahms, "From Creative Action to the Social Rationalization of the Economy: Joseph Schumpeter's Social Theory," Sociological Theory, 1995, 13, 1: 1-13. The approach that I adopt in this work suggests that problems issue as well from fast distinctions that Schumpeter makes between 'rational' and 'nonrational' elements of entrepreneurial action, and from syncretic assumptions underlying his views on entrepreneurship and the nature of business cycles and "long waves" of innovative expansion.

diffuse processes of technological and organizational innovation, on the one hand, and entrepreneurial actions, on the other.

OPEN SYSTEMS ORGANIZATIONAL THEORIES

Nearly twenty years have passed since the publication of Kenney's book, the first substantial academic assessment of growth in the field of commercial biotechnology. Many analysts in the social sciences have since taken to tracking the evolution of the industry from a wide variety of perspectives. Among those concerned primarily with the economic and organizational aspects of this development, particularly influential analytical approaches have included transaction cost economics,[49] 'evolutionary' economics,[50] 'neoinstitutional' organizational theory,[51] and sociological network analysis.[52] In the language of organizational studies, all can be classified as 'open systems' theories.[53] That is to say, they conceptualize firms, not

---

[49] See Oliver Williamson, Markets and Hierarchies: Analysis and Antitrust Implications, New York: Free Press, 1975, and "The Economics of Organizations," American Journal of Sociology, 1981, 87: 548-577.

[50] Giovanni Dosi, Technical Change and Industrial Transformation, New York: St. Martin's Press, 1984; Richard Nelson and Sidney Winter, An Evolutionary Theory of Economic Change, Cambridge, MA: Harvard University Press, 1982.

[51] Mary C. Brinton and Victor Nee, eds., The New Institutionalism in Sociology, New York: Russell Sage Foundation, 1998; Geoffrey M. Hodgson, "The Return of Institutional Economics," pp. 58-76 in The Handbook of Economic Sociology, eds., Neil J. Smelser and Richard Swedberg, Princeton, NJ: Princeton University Press, 1994; Walter W. Powell and Paul J. DiMaggio, eds., The New Institutionalism in Organizational Analysis, Chicago: University of Chicago Press, 1991.

[52] Joel M. Podolny, and Karen L. Page, "Network Forms of Organization," Annual Review of Sociology, 1998, 24: 57-76; Walter W. Powell, "Neither Market Nor Hierarchy: Network Forms of Organization," pp. 295-336 in Research in Organizational Behavior, vol. 12, eds., L.L. Cummings and B. Shaw. Greenwich, CT: JAI Press, 1990; Walter W. Powell and Laurel Smith-Doerr, "Networks and Economic Life," pp. 368-402 in The Handbook of Economic Sociology, eds., Neil J. Smelser and Richard Swedberg, Princeton, NJ: Princeton University Press, 1994.

[53] See Nitin Nohria and Ranjay Gulati, "Firms and Their Environments," pp. 529-555 in The Handbook of Economic Sociology, eds. Neil J. Smelser and Richard Swedberg, Princeton, NJ: Russell Sage Foundation, 1994.

as atomized entities engaged in pure economic competition, but rather more like biological organisms that interact with and are shaped by their environments. For human organizations, environments are social and institutional, and, according to open systems theories, not adequately characterized as markets. They are viewed as fields of cooperation, interdependence, and shared cognitive and normative understandings, as well as instrumental exchange and competition.

In the discipline of sociology, 'open systems' theories are indebted, in certain respects, to the 'human relations' and 'natural systems' schools of industrial organization that became influential in the 1940s and 1950s.[54] These programs emphasized informal relations, and not formal structures, as the keys to understanding organizational functioning. 'Open systems' analyses likewise often attend to the informal aspects of organization. The earlier programs, however, tended to focus inquiries narrowly within the boundaries of individual organizations at the expense of attention to ecological conditions. 'Open systems' analyses generally reverse this emphasis, some almost entirely by attempting to predict the behaviors and fortunes of firms on the basis of their locations in industrial sectors or organizational fields.[55] Empirical investigations in open systems modes seek to illustrate what Mark Granovetter has called the "embeddedness" of economic action in social relations –

---

[54] See, for example, Elton Mayo, The Social Problems of an Industrial Civilization, Boston: Harvard Business School, 1945; Fritz J. Roethlisberger and William J. Dickson, Management and the Worker, Cambridge, MA: Harvard University Press, 1939; and Philip Selznick, TVA and the Grass Roots: A Study in the Sociology of Formal Organization. Berkeley: University of California Press, 1949.

[55] Studies in the latter mode apply concepts drawn from the 'population ecology' paradigm in biology to the sociological investigation of human organizations. See Michael T. Hannan and John Freeman, "The Population Ecology of Organizations," American Journal of Sociology, 1977, 82: 929-964.

and the classes of social action relevant to organizational theory extend well beyond the conventional categories of economic analysis.[56]

From this starting point, open systems theories of innovation define themselves in opposition to neoclassical equilibrium models of the economic process. Neoclassical theorists typically assume monadic, utility-maximizing actors (whether individuals or firms) operating in conditions of perfect competition, while ignoring problems of access to information and the mediating 'effects' of social relationships and institutions on market behaviors. These traditional assumptions and orientations become particularly problematic when applied to science-driven innovative growth in high-tech fields. Clearly, scientific research conducted in universities and academic research institutions has become a crucial component of economic development in the 20th century. Yet, neoclassical models do not account for the actual generation of new knowledge, and they fail to consider the economic implications of institutional structures in research and development and practical organizational mechanisms for technology transfer. They treat expanded technical capacities issuing from the sciences as public windfalls that become available simultaneously to all competitors in the marketplace. Since 1956, when Robert Solow introduced the idea of a "moving equilibrium" in which the effects of new technologies show up in the economy as improved rates of productivity from labor and other inputs, economists of many

[56] Mark S. Granovetter, "Economic Action, Social Structure, and Embeddedness," American Journal of Sociology, 1985, 91: 481-510.

different stripes have accepted the view that technological advances push the system ahead from the outside.[57]

With this premise regarding technological development anchored firmly in place, important aspects of innovation are invisible from the neoclassical point of view. The evaluation and monopolistic appropriation of new knowledge and techniques are central functions of operations within contemporary high-tech firms. The survival of these organizations hinges on how well they execute such tasks under conditions of uncertainty in dynamic environments. Neoclassical analyses are incapable of handling these complex processes. They are designed to model a systemic equilibrium, the result of competition for control of a given supply of scarce resources. They are thus equipped to treat the sources of innovation that spur economic growth in high-tech fields only as 'exogenous variables.' Even big-time macroeconomic modelers, social scientists who vie for Nobel Prizes and whisper in the ears of princes, have begun to admit that new technologies should not be treated as exogenous inputs to growth. Since unexpected shocks to the U.S. economy in the 1970s (triggered by the war in Vietnam and the oil crisis in the Middle East) spelled the end of Keynesian hegemony, neoclassical ideas have dominated in this sphere. However, as the fundamental importance of post-World War II high-tech industries for national and global economic prosperity in the present and future has become increasingly obvious, many practitioners have come to consider the absence of realistic treatments of innovation a glaring omission in the neoclassical scheme.

---

[57] Robert Solow, "A Contribution to the Theory of Economic Growth," Quarterly Journal of Economics, 1956, 70: 65-94.

'New Growth' theorists, for example, contend that technological innovations cannot be treated coherently as simple functions of demands for labor, capital accumulations, or interest rates in static models.[58] The specialized resources (knowledge and skill) that feed innovation must be generated internally within the economy before they can be applied. They do not simply materialize in the instant of a market command. To account for the phenomenon of technological innovation, 'New Growth' proponents argue that technical advances follow from the asymmetric distribution of knowledge within the economic system and that not all actors are positioned to take advantage of them. On this view, new technologies cannot be considered pure (i.e., costless) public goods. Those who control knowledge and technologies can often partially exclude others from implementing them, and they may derive supernormal returns from their use (although benefits can and do spill over to others). In order to incorporate these facts into abstract models of growth, the neoclassical assumptions of perfect information and perfect competition have to be abandoned, and the neoclassical definition of economy has to be enlarged. Neoclassical economists simply have no means (and what is worse, no need) to conceptualize innovation. They can account for new technologies only after inventions and innovations have become established as resources, tools, or commodities of estimable value. This theoretical deficiency is a direct consequence of the neoclassical propensity to decontextualize economic action. Open systems studies of innovation can be understood as sociologically informed counterparts of 'New

[58] See Paul M. Romer, "The Origins of Endogenous Growth," Journal of Economic Perspectives, 1994, 8, 1: 3-22; and "Why, Indeed, in America? Theory, History, and the Origins of Modern Economic Growth," American Economic Review, 1996, 86, 2: 202-206.

Growth' analysis. They remedy the shortcomings of neoclassical economics by analyzing strategic market behaviors, and a wide range of additional determinants and effects of technological progress, as they appear concretely within ever-changing social, cultural, institutional, and political environments.[59]

TRANSACTION COST ECONOMICS

Transaction cost economics is concerned primarily with the 'governance,' or organizational structure, of economic activity. Forms of governance (markets, bureaucratic hierarchies, or hybrids) are understood from this perspective as products of strategic decisions made by economic actors (individual or collective). In transaction cost economics, it is assumed that actors will automatically make 'rational' choices when they can be identified. These are choices that reduce risks and maximize the efficiency of resource expenditures. To this extent, transaction cost analysis is a thoroughly economistic program. It departs from neoclassical theory, however, in that it examines the actual conditions in which strategic decisions are made. It recognizes that – in real-life economics – problems of information are chronic. Individuals and organizations cannot always calculate risks, and must sometimes act when outcomes are uncertain. The organization of the economy, according to transaction cost theory, is always a reflection of situated, imperfectly informed actions. Advocates of this approach interpret the shapes and relations of

[59] Some suggest, though, that the statistical modeling techniques favored by open systems analysts as empirical methods are not well-suited for representing organizational and technological changes as normatively ordered social processes constituted by situated actions unfolding in real time. See, for example, comments by Arthur L. Stinchcombe in "Weak Structural Data," Contemporary Sociology, 1990, 19: 380-382; and "Work Institutions and the Sociology of Everyday Life," pp. 99-116 in The Nature of Work: Sociological Perspectives, ed. Kai Erikson and Steven Peter Vallas, New Haven, CT: Yale University Press, 1990.

organizations in any economic field as the results of assessments that grounded individual and collective actors have made of their relative positions and chances, and of strategies that they have engaged in light of them. Transaction cost theory explains organizational forms in terms of practical rather than idealized economizing.

In order to account for the ways in which introductions of new biotechnologies have restructured the pharmaceutical industry, transaction costs analysts have focused on 'make-or-buy' decisions confronting organizations that populate the field. Large, established drug companies have had to choose between developing biotech R&D capabilities in-house (a hierarchical form of innovation governance), or, alternatively, accessing new technologies through contractual relations with small entrepreneurial start-ups (i.e., market governance). For their part, small companies conducting R&D, upon reaching a certain stage of maturity, must either proceed with 'forward integration' into manufacturing, marketing, regulatory affairs, and other functions, or turn to larger corporate partners for assistance. Transaction costs studies examine how these collective actors have opted to manage trade-offs between the internal administrative costs of vertical bureaucratic organization, on the one hand, and the risks and uncertainties of market exchanges, on the other. The development of commercial biotechnology has given rise to a complex array of strategic alliances, joint ventures, consortia, and mergers and acquisitions, as firms large and small have attempted to combine complementary assets in various ways in order to accomplish their objectives. From the transaction cost point of view, the evolving structures of competition and cooperation in biopharmaceuticals – the emergence and survival of entrepreneurial ventures, and the responses of established corporations to the new

start-ups and new technologies – are best understood in terms of firms' 'make-or-buy' strategies. These courses of action (whether effective or not) are said to account for the organizational forms and the distinctive configuration of interorganizational relations that characterize the field.[60]

EVOLUTIONARY ECONOMIC THEORIES OF INNOVATION

Evolutionary theories of innovation introduce a similar, but less economistic, and more properly sociological perspective. The evolutionary approach makes explicit use of biological analogies to represent organizational forms and functions within larger 'ecological' settings. It proposes that firms' settled organizational routines and conventions resemble, in a manner of speaking, the inherited genetic templates of biological organisms. In evolutionary accounts of innovation, outcomes are read as the combination of the internal characteristics, dispositions, and competencies of firms with principles of 'natural selection' at work in social 'ecosystems' comprised of technological, economic, institutional, and political dimensions. Mechanisms of selection in these environments include but are not limited to market competition. Adaptive responses of firms to their environments are said to determine the maintenance or abandonment of both established and experimental practices, and, hence, the developmental histories of particular technological designs within discrete organizations and industrial sectors. The sum of

---

[60] See Ashish Arora and Alfonso Gambardella, "Complementarities and External Linkages: The Strategies of Large Firms in Biotechnology," Journal of Industrial Economics, 1990, 37, 4: 361-379; Gary P. Pisano, Innovation Through Markets, Hierarchies, and Joint Ventures, Ph.D. Dissertation, University of California, Berkeley, 1989; Gary P. Pisano, "The Governance of Innovation: Vertical Integration and Collaborative Arrangements in the Biotechnology Industry," Research Policy, 1991, 20: 237-249.

these responses (understood as, say, the conditions of firms in a given environment at any given point in time) are also taken as demonstrations of the relative efficacy, or 'fitness,' of different organizations in the short or long term. In contrast to transaction cost economics, which assumes the 'rationality' of firm behaviors (within the limits of feasible environmental monitoring), evolutionary theories conceptualize firms' strategic gambits as themselves embedded in organizational habits and routines. In this manner, they place greater weight on constraints imposed by firms' internal characteristics, and especially their capacities for adapting, in the moment or over time, to external conditions and contingencies.

Evolutionary theories, unlike others on the menu in economics, reserve a place for concrete processes of technological work in accounts of innovation and the industry structures that support it. In evolutionary studies of biotechnology, research and development processes are treated as integral components of firms' behavioral patterns, and so are available for use as explanatory resources in substantive analyses of real world phenomena. The technical and organizational experience and skill that firms acquire (or not) in the course of R&D activities are listed among the operative causes of events and outcomes in the field. Evolutionary studies are able in this way to portray recent transformations in the pharmaceutical industry as consequences of 'technological discontinuities.' They emphasize the "competence destroying" character of new biotechnologies.[61] From the evolutionary point of view, the appearance of new ventures in the pharmaceutical business can be attributed, in part,

[61] On the Schumpeterian concept of "competence destroying" technical advance, see Michael Tushman and Philip Anderson, "Technological Discontinuities and Organizational Environments," Administrative Science Quarterly, 1986, 31: 439-465.

to the capacity of biotechnologies to outperform and perhaps make obsolete established techniques of drug production.[62] The persistence of small companies against countervailing economic forces in the field is explained by benefits accruing to the control of these new scientific resources. Through the development of organizational instruments for tapping and cultivating advances in academic bioscience, the new firms have been able to exempt themselves from the industry's established economies of scale, and to leverage their survival when entering into partnerships with larger, richer corporations. For all of the disadvantages associated with small size and undercapitalization, entrepreneurial start-ups in this field have enjoyed a head start in the development of biotechnologies. Because their organizational 'genotypes' and 'phenotypes' have been constituted in the recombination of practices from both academic and commercial settings, the new firms have been uniquely equipped to develop and sustain innovative biopharmaceutical programs.[63] Evolutionary theories have incorporated the organizational procurement and utilization of scientific and technological skills into descriptions of how new biotech companies and their larger competitors behave and fare in the markets, organizational fields, and larger institutional contexts that

---

[62] The traditional approach is often described by those in the drug business as 'empirical' rather than 'rational.' In the 20th century, commercial drug discovery has consisted primarily in the mass screening of chemical compounds for pharmacological activity. Investigations proceed from this more or less random search to the chemical reformulation of candidate compounds that exhibit desired characteristics or effects. The word 'rational,' by contrast, is used to describe drug discovery and development processes that begin from an established base of knowledge regarding specific materials, chemical or biological, and the means by which they might be transformed into safe, effective medicines. In this context, it would be a mistake to interpret the terms 'empirical' and 'rational' in the manner of philosophers of science. Both refer to methods informed by practical experience.

comprise the pharmaceutical industry.[64] This affords them a decided advantage over economic programs that neglect to do so.

SOCIOLOGICAL NETWORK ANALYSIS

In the discipline of sociology, no recently devised program of research has generated more excitement, optimism, or empirical inquiries than social network analysis. Seminal works in this area include Mark Granovetter's famous writings on job markets.[65] Granovetter showed that individuals are afforded certain opportunities and prevented from recognizing or taking advantage of others because they travel in specific, delimited social circles. For analytical purposes, the patterned interactions that constitute these social spaces can be conceptualized as networks with two-dimensional structures. Granovetter surmised that as the shapes of networks vary, that is, as the quantity and quality of the relationships that they represent differ, so do individuals' options and chances vary and differ. In the case of labor market mobility and choice, he found that participation in sparse, expansive networks composed of numerous "weak" ties (e.g., casual acquaintances) generally offers actors greater

---

[63] Obviously, the biological analogy has limits. Organizational environments are social, cultural, economic, and political, as are the 'mechanisms' that produce recombinations and mutations of organizational codes.

[64] See Ashish Arora and Alfonso Gambardella, "Evaluating Technological Information and Utilizing It: Scientific Knowledge, Technological Capability, and External Linkages in Biotechnology," Journal of Economic Behavior and Organization, 1994, 24: 91-114; Steven W. Collins, "Genes, Markets, and the State: The Emergence of Commercial Biotechnology in the United States and Japan," Ph.D. Dissertation, University of Virginia, 1994; Alfonso Gambardella, Science and Innovation: The U.S. Pharmaceutical Industry During the 1980s, Cambridge: Cambridge University Press, 1995, esp. ch. 6; Maureen D. McKelvey, Evolutionary Innovations: The Business of Biotechnology, Oxford: Oxford University Press, 1996; and Luigi Orsenigo, The Emergence of Biotechnology: Institutions and Markets in Industrial Innovation, New York: St. Martin's Press, 1989.

[65] Mark S. Granovetter, "The Strength of Weak Ties," American Journal of Sociology, 1973, 78, 6: 1360-1380; and Getting a Job: A Study of Contacts and Careers, Cambridge, MA: Harvard University Press, 1974.

flexibility than participation in networks composed of dense, concentrated "strong" ties (those that encourage 'endogenous' patterns of interaction). In short, Granovetter confirmed what is summarily expressed in the old adage 'it's who you know that counts.'[66] Recent sociological studies of innovation in biotechnology and the pharmaceutical industry have shown that firms in high-tech industries derive the same benefits from networking; in fact, these works represent firms and high-tech industries as networks in organizational form, while confirming the crucial importance of interfirm linkages and alliances for effective competition and survival in clustered, globalized, 'scale free' information economies.[67]

The implications of selecting network associations as the relevant point of departure for social research, however, extend far beyond any particular substantive conclusion. The popularity of the network approach can be attributed to the fact that it has enabled social researchers to stretch their empirical reach to include a broad range of general social phenomena that were not previously well-defined. Through the application of network concepts, researchers have been able, or so they have claimed, to specify mechanisms by which culture is diffused in social and geographic space, and to link the social phenomena of mimicry, contagion, influence, and power with definite patterns of interaction. Historically, these concepts have been among the most

---

[66] Of course, when people say 'it's who you know that counts,' they are not necessarily referring to specific individuals (say, for example, those to whom one is strongly tied). They might just as well be making a general theoretical statement. When the latter is the case, it is implied that who counts, who doesn't, and for what purposes, depends on circumstances at hand, and also that those who matter may include persons to whom one is only loosely connected.

[67] See Albert-László Barabási, Linked: The New Science of Networks – How Everything is Connected to Everything Else and What it Means for Science, Business, and Everyday Life, Cambridge, MA: Perseus, 2002, pp. 206-209.

slippery for sociologists to handle. In the methodological toolkit of the network paradigm are instruments that permit the sources and effects of such elusive phenomena to be identified and measured with greater precision in observable social structures. Applications of network analytic techniques to these phenomena have thus enriched explanations of social action in many different substantive subfields.[68] Investigators researching social movements and economic and organizational processes have especially favored this approach. In every instance, the objective has been to understand actions and events, whether the doings and travels of individuals or the performances and fortunes of organizations, in terms of the larger webs of association and interdependence in which actors are enmeshed.

The enhanced explanatory power of network analysis derives from the manner in which it dissolves a long-standing logical conundrum in social theory. As well as a methodological approach, the network perspective embodies a structural theory of action that manages to avoid (in certain formulations) both the determinism of prior functionalist models that incorporated 'oversocialized' conceptions of the actor, and the economic reductionism of neoclassical and rational choice schemes that assume for analytical purposes only 'undersocialized' utility maximizers.[69] In the theoretical

---

[68] See David Strang and Sarah A. Soule, "Diffusion in Organizations and Social Movements: From Hybrid Corn to Poison Pills, " Annual Review of Sociology, 1998, 24: 265-290.

[69] For a trenchant critique of 'overenthusiastic' sociology, see Dennis Wrong, "The Over-Socialized Conception of Man in Modern Sociology," American Sociological Review, 1961, 26: 183-193. Wrong rightly appealed to Freudian ideas to counter Talcott Parsons' depiction of homo sociologicus. For trenchant critiques of 'overenthusiastic' economics, see Talcott Parsons, The Structure of Social Action, New York: McGraw-Hill, 1937; and Talcott Parsons and Neil J. Smelser, Economy and Society: A Study in the Integration of Economic and Social Theory, Glencoe, IL: Free Press, 1956. Parsons eventually incorporated Freudian ideas into a model of the "personality system" – although not rightly from the Wrong point of view – in order to round out his sociological alternative to homo economicus. See Talcott Parsons, Social Structure and Personality, New York: Free Press of Glencoe, 1964.

imagery of network analysis, social action is situated in spheres of circumscribed agency, network niches or nodes comprised of particularized sets of capacities and constraints. The advantages and liabilities of these positions become defined in time and social context as networks take shape and evolve around them. From the perspectives of niched or noded actors, network structuring processes generate continually changing, but always bounded, horizons of possibility.[70] With this conceptualization, the network approach does away with a fundamental problem of explanation that contemporary sociology has inherited from its classical theories: how to manage in substantive accounts the opposition of social structure and human agency. In network analysis, the concepts of structure and agency are integrated empirically into the same theoretical scheme. Network analytic techniques harness sufficient intellectual horsepower to represent at the level of concrete interactions both the exercise of voluntary choice and degrees of freedom and constraint defined by social conditions and circumstances.[71]

---

[70] See Harrison White, Identity and Control: A Structural Theory of Social Action, Princeton, NJ: Princeton University Press, 1992.

[71] Critics have argued cogently that this is accomplished through the reification of network positions, an operation that endows social locations and not actions with causal properties. For an exhaustive theoretical exposition on problematic treatments and deliberate omissions of human agency in sociometric network approaches that posit the "structural equivalence" of actors (i.e., people), see Mustafa Emirbayer and Jeff Goodwin, "Network Analysis, Culture, and the Problem of Agency," American Journal of Sociology, 1994, 99: 1411-1451. Emirbayer and Goodwin contend that without adequate attention paid to parts played by individual choices, motives, and commitments to cultural values, network studies will not be able to account for "the formation, reproduction, and transformation of social networks themselves" (p. 1413). From a point of view pertinent to the disciplinary interests of network analysts, however, they miss the point. In structural network analysis, networks are obviously self-organizing. They form, reproduce, and transform themselves (and so, in the study of social networks from this perspective, it is not necessary or profitable to inquire about people's motives, intentions, or values).

The network approach is a flexible one. It permits researchers to conduct investigative affairs at multiple levels of abstraction. Network maps cut across different levels of analysis simultaneously, supplying researchers with a method of tying together micro, meso, and macro theoretical spheres by empirical means. Persons or collectives may be designated as network constituents. Patterns of association among persons are studied in order to derive information about organizational processes. Investigations of organizational networks ratchet the theoretical apparatus up to the level of corporate actors. They examine how aggregate structures of interorganizational links regulate the behaviors of collective entities. In principle, mapping links across organizational fields brings into view even broader macrosocial institutional environments. And with yet another abstractive leap, the topics that occupy students of international relations, global political economy, or 'world systems' analysis could be translated into the network idiom. At every level, networks appear to exhibit emergent properties that channel individual and corporate behaviors 'from above,' so to speak. Network analytic techniques are thus appropriate for investigating social processes of any form or magnitude. This is so because, as Podolny and Page comment in a review of efforts to understand the functioning of social networks in organizations and organizational fields: "...from a structural perspective, every form of organization is a network."[72]

---

[72] Joel M. Podolny and Karen L. Page, "Network Forms of Organization," Annual Review of Sociology, 1998, 24: 57-76; quote on p. 60. This fact begs questions about the discursive and prediscursive experiential foundations of structural theorizing in organizational sociology. For instance, how is it possible for network analysts to reduce to sameness concepts (e.g., organizational types) that are distinguished in other theories? What is implied about the ontological character of the objects 'explained' or 'covered' in organizational theories (e.g., persons, behaviors, social interactions) if these concepts can be so reduced? What makes the reductions plausible? What makes the differentiated higher order concepts (i.e., organizations) intelligible?

Some network analysts focus exclusively on the architectures of network formations, and the effects that particular network configurations visit on actors (individuals or collectives) positioned variously within them.[73] Working from decontextualized blueprints of network ties, they attempt to uncover the ways in which structures of association determine outcomes of social processes. For instance, 'population ecology' studies of organizations have adopted network modeling techniques in order to characterize mechanisms of 'natural selection' in organizational fields. In the case of business firms, such studies attempt to show how locations in interorganizational networks dictate the ways in which companies may respond strategically to market conditions and the demands of competition.[74] These locations can limit the range of autonomous actions that firms may engage, but they simultaneously provide companies with access to resources necessary for the exercise of goal-oriented action. Research on the positioning of corporate actors in network niches or nodes can perhaps provide useful information on the character and purposes of interfirm alliances once stable patterns of association have been established (and maybe, to some extent, for as long as these patterns are sustained in some recognizable manner).

---

[73] Well-known efforts to elaborate and boost the predictive capabilities of the network paradigm in this direction include, Ronald S. Burt, Structural Holes: The Social Structure of Competition, Cambridge, MA: Harvard University Press, 1982, and Toward a Structural Theory of Action: Network Models of Social Structures, New York: Academic Press, 1992; and Harrison White, Identity and Control: A Structural Theory of Social Action, Princeton, NJ: Princeton University Press, 1992.

[74] See Michael T. Hannan and John Freeman, "The Population Ecology of Organizations," American Journal of Sociology, 1977, 82: 929-964; Walter W. Powell, Douglas R. White, Kenneth W. Koput, and Jason Owen-Smith, "Network Dynamics and Field Evolution: The Growth of Interorganizational Collaboration in the Life Sciences," American Journal of Sociology, forthcoming, 2004.

Many other network studies have been conducted to pursue themes associated with the 'new institutionalism' in organizational analysis.[75] Works of this kind explore the significance of social networks as a distinctive type of organizational governance. Unlike most programs of research in economics (the evolutionary approach is a notable exception), network analyses drawing on neoinstitutionalism are concerned with the ways in which social associations and processes constitute a transparent cultural backdrop for activities that appear in many economists' models as instances of 'purely' rationalized calculation and exchange. They attempt to demonstrate that network associations modify the workings of markets, presenting opportunities to and imposing normative constraints on individuals and organizations beyond those that conventional economic analyses are equipped to recognize. The network as a normative form of governance is said to modulate purely instrumental strategic decision-making. In 'networked organizations,' the basis of interaction and exchange consists in trust and loyalty, mutual obligations to forgo opportunism, and norms of reciprocity, as well as formal contractual agreements. In such organizational settings, sustaining relationships may take precedence over profits or efficiency. Ethical participation in network relationships may, in fact, be a necessary precondition for profit-making or efficiency. For this reason, many organizational theorists contend that network forms of organization differ qualitatively from markets and bureaucratic

---

[75] Mary C. Brinton and Victor Nee, eds., The New Institutionalism in Sociology, New York: Russell Sage Foundation, 1998; Paul J. DiMaggio and Walter W. Powell, "The Iron Cage Revisited: Institutional Isomorphism and Collective Rationality in Organizational Fields," American Sociological Review, 1983, 48: 147-160; John W. Meyer and Brian Rowan, "Institutionalized Organizations: Formal Structure as Myth and Ceremony," American Journal of Sociology, 1977, 83: 340-363; Walter W. Powell and Paul J. DiMaggio, eds., The New Institutionalism in Organizational Analysis, Chicago: University of Chicago Press, 1991.

hierarchies. Networks are not hybrids of markets and hierarchies but distinctive forms in their own right.[76]

This branch of network analysis also shares with evolutionary economic theories a focus on the cognitive dimensions of social organization. It, too, is concerned with routinized practices, and the shared, deeply-ingrained, taken-for-granted cultural understandings that permit organizational activities to be conducted in more or less orderly ways as a matter of course. Consequently, network analyses testing neoinstitutional ideas devote greater attention to the content of network links, the normative substance of network relationships, social differences among network constituents, and the concrete functions that network connections serve in the maintenance of social organizations and institutions. Investigations of these phenomena are conducted at various levels of analysis. Some examine the adoption of practices by individual organizations; others are concerned with broader social logics that define organizational fields. Neoinstitutional organizational theory is built on the idea that some measure of normative and ideological cohesiveness is ordinarily a precondition for the reproduction of social structures and institutions. On this view, the maintenance of a social order depends on the perceived legitimacy, by at least some of its members, of the institutions and structures of authority that constitute it. From this perspective, organizational life is understood to be imbued with collectively recognized meanings and values. And in business, to cite just one important sphere of

---

[76] Walter W. Powell, "Neither Market Nor Hierarchy: Network Forms of Organization," pp. 295-336 in Research in Organizational Behavior, vol. 12, eds., L.L. Cummings and B. Shaw, Greenwich, CT: JAI Press, 1990. Notions of 'pure instrumentalism' and 'strict organizational formality' perform indispensable conceptual and rhetorical functions in arguments of this kind.

organized activity, the attributes and operations of firms are understood to carry symbolic as well as functional significance. Network studies have been employed to characterize the mechanisms or channels of communication through which conventional understandings and values are established and institutionalized within organizational and industrial fields.

By and large, network studies of the biotechnology industry have been focused on firm-level phenomena. They seek to explain the histories of biotech companies in terms of these firms' positions in networks of exchange, competition, and cooperation, while devoting attention to the functions as well as the forms of interorganizational networks in the field. They attempt to understand the operational practices and strategic maneuverings of biotech and pharmaceutical companies as products of interfirm alliances, both formal and informal. The objective is to show how the repertoires of action on which biotech companies draw as they attempt to negotiate passages through organizational fields and competitive markets have been formulated, signaled, and utilized within processes of interorganizational networking.[77] Some analysts have made use of network concepts to address the noninstrumental, 'nonrational' cultural dimensions of commercial biotech activity. They look to the normative and ideological aspects of firms and their environments (and especially the

[77] Loet Leydesdorff and Gaston Heimeriks, "The Self-Organization of the European Information Society: The Case of Biotechnology," Journal of the American Society for Information Science and Technology, 2001, 52, 14: 1262-1274; Luigi Orsenigo, Fabio Pammoli, and Massimo Riccaboni, "Technological Change and Network Dynamics: Lessons from the Pharmaceutical Industry," Research Policy, 2001, 30, 3: 485-508; Jason Owen-Smith, Massimo Riccaboni, Fabio Pammoli, and Walter W. Powell, "A Comparison of U.S. and European University-Industry Relations in the Life Sciences," Management Science, 2002, 48, 1: 24-73; Walter W. Powell and Jason Owen-Smith, "Universities and the Market for Intellectual Property in the Life Sciences," Journal of Policy Analysis and Management, 1998, 17, 2: 253-277.

social networks that constitute them) in order to account for the diffusion and maintenance of organizational practices. The phenomena of interest in these studies have been the social and cultural dimensions of the networking processes in which biotechnologies have been validated and corporate reputations established legitimated, and in which the industry's peculiar financial, managerial, and organizational conventions have been transmitted and reproduced.[78] But no topic has received more attention from network analysts than the means by which biotech companies have made and managed technical innovations.

Of special interest for network analysts working in this area has been the sourcing of information and skill by biotech enterprises through formal and informal interorganizational ties. The basic insight that network-based approaches to the study of technological research and development seek to advance is that the sources of innovation do not reside entirely within organizational boundaries. Innovation is depicted, instead, as a process facilitated by the transmission of knowledge and materials between organizations. The formal confines of organizations may be significant to the extent that internal activities promote or inhibit the formation of ties with external entities, and positively or negatively affect the utilization of inputs from external sources. These boundaries are assumed, however, to be highly permeable, especially in the case of high-tech firms in emerging technoregions. Further, the firm

---

[78] See James E. Gail, "Strategic Alliances as 'Virtual Integration': A Longitudinal Study of Biotech Industry-Level Learning," Academy of Management Journal, Best Paper Proceedings, 1995: 469-473; Toby E. Stuart, Ha Hoang, and Ralph C. Hybels, "Interorganizational Endorsements and the Performance of Entrepreneurial Ventures," Administrative Science Quarterly 1999, 44, 2: 315-349; cf. Lynne G. Zucker and Michael R. Darby, "Individual Action and the Demand for Institutions," American Behavioral Scientist, 1997, 40, 4: 502-513.

as a discrete entity featuring particularized internal characteristics is understood to be influenced to a significant degree by its history of external relationships.[79] Numerous network studies have explored how the acquisition of knowledge and experience through participation in interorganizational networks effects firm growth or recession.[80]

Many questions remain unanswered in this area. For example, social researchers conducting management and organizational studies have reported that informal modes of information trading are ubiquitous in high-tech industry and contribute significantly to the making of innovations.[81] Others have found that open

---

[79] See Lynne G. Zucker, et al., "Collaboration Structure and Information Dilemmas in Biotechnology: Organizational Boundaries as Trust Production," Working Paper #5199, National Bureau of Economic Research, Cambridge, MA, 1995.

[80] Joel A.C. Baum, Tony Calabrese, and Brian S. Silverman, "Don't Go It Alone: Alliance Composition and Startups' Peformance in Canadian Biotechnology," Strategic Management Journal, 2000, 21, 3: 267-294; Wesley M. Cohen, Richard R. Nelson and John P. Walsh, "Links and Impacts: The Influence of Public Research on Industrial R&D," Management Science, 2002, 48, 1: 1-23; David L. Deeds and Charles W.L. Hill, "Strategic Alliances and the Rate of New Product Development: An Empirical Study of Entrepreneurial Biotechnology Firms," Journal of Business Venturing, 1996, 11: 41-55; Julia Porter Liebeskind, et al., "Social Networks, Learning, and Flexibility: Sourcing Scientific Knowledge in New Biotechnology Firms," Organization Science, 1996, 7, 4: 428-433; Amalya L. Oliver and Julia Porter Liebeskind, "Three Levels of Networking for Sourcing Intellectual Capital in Biotechnology," International Studies of Management and Organization 1997-1998, 27, 4: 76-103; Jason Owen-Smith and Walter W. Powell, "Knowledge Networks as Channels and Conduits: The Effects of Formal Structure in the Boston Biotechnology Community," Organization Science, 2004, 15, 1: 5-21; Walter W. Powell, "Learning from Collaboration: Knowledge and Networks in the Biotechnology and Pharmaceutical Industries," California Management Review, 1998, 40, 3: 228-240; Walter W. Powell, Kenneth W. Koput, and Laurel Smith-Doerr, "Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology," Administrative Science Quarterly, 1996, 41: 116-145; Walter W. Powell, Kenneth W. Koput, Laurel Smith-Doerr, and Jason Owen-Smith, "Network Position and Firm Performance: Organizational Returns to Collaboration in the Biotechnology Industry," pp. 229-254 in Research in the Sociology of Organizations, vol. 16, eds. Steven Andrews and David Knoke, Stanford, CT: JAI Press, 1999; Weijan Shan, Gordon Walker, and Bruce Kogut, "Interfirm Cooperation and Startup Innovation in the Biotechnology Industry." Strategic Management Journal, 1994, 15: 387-394; Lynne G. Zucker, Michael R. Darby, and Jeff Armstrong, "Commercializing Knowledge: University Science, Knowledge Capture, and Firm Performance in Biotechnology," Management Science, 2002, 48, 1: 138-153.

[81] See, for example, Stephen Schrader, "Informal Technology Transfer Between Firms: Cooperation Through Information Trading," Research Policy, 1991, 20, 2: 153-170; and Eric von Hippel, The Sources of Innovation, New York: Oxford University Press, 1988.

labor markets (those that permit individuals high degrees of mobility) facilitate this kind of exchange, and are conspicuous features of new regional high-tech growth clusters.[82] Due to the proximity of many relevant 'alters' in these clusters, 'egos' are able to establish and maintain extensive personal contacts. These connections enable people to move more or less freely between local organizations and institutions. They are also, apparently, important channels of information and technology transfer in such settings. While in certain respects these informal associations may make life more difficult for companies seeking to appropriate returns on knowledge and prevent losses of strategically valuable information, they also help to explain the high rates of innovation often found in technoregions that are densely populated geographically by firms that are loosely interwoven socially. The evidence supporting the importance of informal trading has been drawn mainly from case studies. Network analysis may prove a useful tool for charting systematically the dynamics of this phenomenon.[83] Tracking the social mobility of knowledge by monitoring travels of persons within organizational fields like the biotech industry, and theorizing the relationships between social mobility and rates of innovation, will no doubt continue to challenge and

---

[82] See, for example, Everett M. Rogers and Katherine Larsen, Silicon Valley Fever: The Growth of High Technology Culture, New York: Basic Books, 1984; and AnnaLee Saxenian, Regional Advantage: Culture and Competition in Silicon Valley and Route 128, Cambridge, MA: Harvard University Press, 1994.

[83] Structural network researchers have examined relationships between firm productivity and various kinds of interorganizational relationships in biotechnology, e.g., university-industry interactions (see Zucker and Darby, "Intellectual Capital and the Birth of U.S. Biotechnology Enterprises," Working Paper #4653, National Bureau of Economic Research, Cambridge, MA, 1994), but they have yet to correlate mathematically rates of innovation and the characteristics of labor markets in the field. Given the prevailing methodological values in the field, a pressing task for structural network analysts must be the confirmation of these relationships, without which understandings of innovation will remain (within the 'paradigm') speculative, fragmentary, and deficient.

occupy structural network analysts as they move boldly forward into the new millenium.

So, to sum up: contemporary open systems studies of the biotechnology industry, as their authors advertise, employ sophisticated methods. They feature novel, progressive analytical vocabularies. In applying these tools, open systems analysts have attempted to deliver rich and unique insights into the functioning of high-tech organizations. For example, in a masterful, ground-breaking open systems network study, Zucker and Darby have discovered that firms working with accomplished, productive, and well-connected bioscientists tend to outperform those that do not. On balance, these companies have been more successful. They are likely to employee more people and to have more products in development and on the market.[84] In addition to valuable empirical generalizations of this kind, network studies of biotechnology have begun pioneering new theoretical territories in the social scientific understanding of high-tech innovation. Powell, Koput, and Smith-Doerr, for instance, have tested and confirmed hypotheses that, in sum, support the following theoretical conclusion: when the resources necessary for innovation in a technological field are complex, expanding, and widely dispersed, as is the case in biotechnology, then firms that access and learn how to use these resources will be better positioned to innovate and grow than those that fail to do so.[85] Network concepts draw analytical

---

[84] See Lynne G. Zucker and Michael R. Darby, "Virtuous Circles of Productivity: Star Bioscientists and the Institutional Transformation of Industry," Working Paper #5342, National Bureau of Economic Research, Cambridge, MA, 1995. The practical maxim to be derived from this research, I guess, is 'work with people who know what they're doing.'

[85] These resources must be acquired by establishing connections and trading with other organizations. See Walter W. Powell, Kenneth W. Koput, and Laurel Smith-Doerr, "Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology," Administrative Science

attention to social processes spanning organizational boundaries, and so permit and facilitate the confirmation of these sorts of facts and theoretical summaries.

Gary P. Pisano draws complementary conclusions using different open systems concepts. In an empirical application of transaction cost theory, he formulates and tests hypotheses that incorporate evolutionary premises regarding the behaviors of firms with evidence drawn from the biotechnology industry.[86] Among the theoretical implications emerging from this study is the idea that when technological innovations appear within organizational fields, firms' capabilities and propensities, as well as their more tangible assets, will, in conjunction with transaction cost factors, influence the restructuring of industrial governance. As Pisano says, "conditions that make R&D contracting hazardous can be expected to create competition rather than cooperation between new entrants [that control an innovation] and established firms [that want it]."[87] Under such conditions, firms will likely do well if they possess the capacity for 'forward integration' into their areas of need. When conditions make contractual agreements less risky, Pisano predicts that "cooperation between vertically or functionally specialized firms...may evolve."[88] When this is the case, companies that can muster the wherewithal to manage collaborations effectively will be better

---

Quarterly, 1996, 41: 116-145. The take home point in this article, apparently, is that firms positioned and prepared by chance or design for high-tech success will likely outperform those that are not so prepared.

[86] Gary P. Pisano, "The R&D Boundaries of the Firm: An Empirical Analysis," Administrative Science Quarterly, 1990, 35: 153-176.

[87] Pisano, "The R&D Boundaries of the Firm," p. 174.

[88] Pisano, "The R&D Boundaries of the Firm," p. 174. The practical lesson, restated, for those directing companies old or new, large or small, is this: when cooperation seems unwise, compete; when competition appears unwise, cooperate.

bets to survive and prosper. Pisano's conclusions are representative of the kind of insights that recent organizational studies have produced.

Because of recent developments in open systems analysis, organizational theorists report that great strides have lately been made in their specialty. It seems that organizational theorizing is much better now than it used to be. After apparently going around in circles for decades – as organizational theorists Nohria and Gulati have described it – shifting from the concrete to the abstract, from the material to the ideal, and back again, in vain attempts to capture the essence of human organization, the field is now setting aside false dichotomies and charting a bold new course that many expect to usher in an era of unprecedented cumulative advances.[89] Some practitioners assert that, through the continuing refinement of their conceptual and empirical tools (and, it might be added, the maintenance of communicative practices that set the enterprise apart from the world of everyday discourse), they have positioned themselves to derive general theoretical knowledge of organizational cohesion, coordination, competition, and conflict that will surpass, in both quality and quantity, that which was known to previous generations.[90] The integration and

---

[89] Reviewing the history of organizational theory, which they partition into four major phases since its inception around the turn of the century, Nohria and Gulati observe: "...the focus in the first stage was entirely on the formal organization structure. In the second stage, the emphasis shifted dramatically, and a great deal of importance was attached to the informal organization. In the third stage the emphasis shifted back to the formal organization. Recently, the informal organization has again become fashionable as the bureaucratic structure that had been the orienting framework for the formal organization throughout this century has come under increasing attack." See Nitin Nohria and Ranjay Gulati, "Firms and Their Environments," pp. 529-555 in The Handbook of Economic Sociology, eds. Neil J. Smelser and Richard Swedberg, Princeton, NJ: Russell Sage Foundation, 1994.

[90] Podolny, Stuart, and Hannan, for instance, suggest that their ecological network approach, which assesses the effects of firm location in structures of interorganizational linkages, "opens up the possibility for a general sociological theory of competition." See Joel M. Podolny, Toby E. Stuart, and Michael T. Hannan, "Networks, Knowledge, and Niches: Competition in the Worldwide Semiconductor Industry, 1984-1991," American Journal of Sociology, 1996, 102, 3: 659-689.

synthesis of multiple open systems perspectives in recent studies of biotechnology are presented as works that exemplify this promise. Audiences surveying up-to-date open systems literatures on the social organization of the biotechnology industry will begin to see the 'big picture' of the field come into view.

Still, for all of their merits, and for all of the practical wisdom that they have developed, open systems approaches have failed to capture fully the innovative dimensions of commercial bioscience. While the biotechnology industry continues in the present to comprise a locus of significant entrepreneurial activity, economists and sociologists examining the field still pay only scant attention to entrepreneurs.[91] They note, of course, that the story of commercial biotechnology is in important ways a story of entrepreneurial actions, but entrepreneurial initiatives play no substantive role in their explanatory models. Economic and sociological studies of innovation directed specifically to the formation of new ventures rarely proceed beyond the correlation of start-up rates or measures of firm productivity with various structural indicators or explanatory variables.[92] Works that explicitly link the historical origins of the field to later developments do so by resorting to creation myths that conjure up abstract forces

---

[91] The entrepreneurial activities of scientists and their partners are naturally topics of abiding interest for those studying university-industry relations (see ch. 10 below). In this area, however, the primary concern has been the implications of such doings for academic institutions, e.g., in the transfer of technologies, the generation of revenues, the possible corruption of science, or the siphoning of public knowledge by private interests. The nuts and bolts of entrepreneurial venturing are rarely examined.

[92] See, for example, Edward J. Delaney, "Technology Search and Firm Bounds in Biotechnology: New Firms as Agents of Change," Growth & Change, 1993, 24, 1: 206-228; Ray Oakey, Wendy Faulkner, Sarah Cooper, and Vivien Walsh, New Firms in the Biotechnology Industry: Their Contribution to Innovation and Growth, London: Pinter, 1990; Lynne G. Zucker, Michael R. Darby, and Marilynn B. Brewer, "Intellectual Capital and the Birth of U.S. Biotechnology Enterprises," Working Paper #4653, National Bureau of Economic Research, Cambridge, MA, 1994; Lynne G. Zucker and Michael R. Darby, "Individual Action and the Demand for Institutions," American Behavioral Scientist, 1997, 40, 4: 502-513; cf. Edward J. Malecki, "What About People in High Technology? Some Research and Policy Considerations," Growth and Change, 1989, 20, 1: 67-79.

at work in science and industry. They invoke as explanatory resources things like 'technological discontinuities' or what might be described as the Aristotelian properties of capital that cause it to find its way unerringly to profit opportunities. In principle, there is nothing wrong with employing these concepts. In practice, however, they are often granted an ontological status that burdens them with more explanatory weight than they can bear. The consequences for organizational studies are apparent in recent investigations of the biotechnology business. Satisfied to lean on received theoretical interpretations of the origins and innovative dynamics of biotechnologies as formulated by Kenney and others pursuing similar projects, economists and organizational sociologists have moved ahead in the study of an entrepreneurial field without ever having examined in detail the phenomenon of entrepreneurship within it.

Only lately have students of organizations begun to acknowledge the liabilities of this analytical strategy. In editing and contributing to a recent collection of essays and reports of research on Silicon Valley (as a site of high-tech innovation, including biotechnological progress) Kenney himself adopts an approach in which entrepreneurs are pushed a bit closer to the front and center of the stage. In a theoretical chapter, he proposes, along with Urs Von Burg, that Silicon Valley is unique in its capacity to generate recurring waves of technological innovation and wealth creation because it features two distinct (although interrelated) economies.[93] The first is comprised of a more or less conventional grouping of firms, suppliers, research institutions, and so

[93] See Kenney and Von Burg, "Institutions and Economies: Creating Silicon Valley," pp. 218-240 in Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000.

on. These organizations contribute material, technical, and human inputs to the design and manufacture of innovative products and processes. The second economy is an institutional infrastructure dedicated specifically to the formation and growth of new firms. According to Kenney and Von Burg, the vitality of this second economy is what sets Silicon Valley apart as a locus of technological and economic progress. The fundamental "inputs" to this second economy, they say, are "entrepreneurs, their ideas, and their efforts."[94] Here, the authors acknowledge that institutions, organizations, and economies are animated by individuals, and that the origins of broad social movements can, at least in the case of contemporary technological change, be traced to the actions of particular persons. Their inclusion of a few suggestive anecdotes seems implicitly to endorse the idea that the best explanations of contemporary high-tech innovation are historical and biographical.[95] Nevertheless, Kenney and Von Burg simultaneously imply that the careers and histories of individuals are mostly irrelevant to explanations of technical and organizational change in Silicon Valley. They are satisfied, apparently, to take the supply of entrepreneurs for granted as a feature of the region's institutional ecology: "[i]n this venue it is not necessary to dwell on the various social or psychological dimensions of entrepreneurship; it is sufficient that there be a constant flow of entrepreneurs."

---

[94] Kenney and Von Burg, "Institutions and Economies: Creating Silicon Valley," p. 219.

[95] In the introduction to the book, Kenney informs readers that his "only editing bias was to encourage contributors to truncate long theoretical sections in favor of more empirical material." In other words, he preferred contributions to be longer on stories, shorter on abstractions. See "Introduction," pp. 1-12 in Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000, p. 2.

In another essay from the same volume, Kenney and Richard Florida identify the venture capital industry as a key component of the Valley's innovation infrastructure.[96] To articulate the roles of venture capitalists in new firm formation, the authors draw special attention to individual pioneers and other influential personages. Without apology, for one chapter, at least, they grant theoretical priority to individual actions and decisions, and, in so doing, they adopt a narrative approach to explanation. Elsewhere, however, Kenney partially withdraws the credit that he and Florida award to individual venture capitalists. With Von Burg, he says: "Despite our emphasis on the socioeconomic institutions [including the venture capital business], we recognize that this entire economy of institutions and organizations dedicated to start-ups is possible only because the underlying electronics and biomedical technologies are improving so quickly."[97] Here, science and technology are again identified as the fundamental drivers of economic and organizational change. Entrepreneurs and their friends and helpers merely take advantage of the opportunities that science and technology generate. Kenney's analytical distinction between science and technology, on the one hand, and business and social life, on the other, may be useful for certain purposes, but scientific and technological advances are not independent (i.e., 'extrasocial') forces. Science and technology are collective activities. They are social and cultural phenomena, and products of organized human

---

[96] Martin Kenney and Richard Florida, "Venture Capital in Silicon Valley: Fueling New Firm Formation," pp. 98-123 in Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000.

[97] Kenney and Von Burg, "Institutions and Economies: Creating Silicon Valley," p. 219.

labor. And, in Silicon Valley and similar 'entrepreneurial regions,'[98] technological innovation and organizational engineering are often two sides of the same coin. Scientists and technologists become entrepreneurs and executives – this is a hallmark of places like Silicon Valley – and sometimes they become venture capitalists or business consultants as well.[99] In the section that follows, I introduce an academic literature that understands sciences and technologies as social institutions. This approach cuts through the conceptual confusion that sometimes ensues when theoretical writings on technological and organizational innovation invoke abstract causes and effects.

HETEROGENEOUS ENGINEERS AND SELF-FULFILLING PROPHECIES

Reports on the biotechnology business framed in the lexica of the 'open systems' approaches cited above make for fascinating reading. It's hard to put them down. For those sufficiently familiar with their proprietary rhetorical conventions, it is possible to discern within them many veridical statements on the character of contemporary bioscientific practices in commercial settings. Nevertheless, in this work, in order to craft a rather different interpretation of happenings in the formation of San Diego's biotechnology industry, I draw liberally from conceptual tools

---

[98] There is no denying the uniqueness of Silicon Valley or the problems attending efforts to reproduce its successes in places with different histories, but there are other regions that resemble it in important ways. San Diego's 'Biotech Beach' is but one example. Clusters of high-tech innovation located in Boston, Seattle, Washington, D.C., Austin, Texas, and North Carolina's Research Triangle, are others.

[99] Venture capitalists, too, sometimes become executives – Genentech's Robert Swanson was the prototype. See Ralph T. King, Jr., "Genentech's Robert Swanson, a Pioneer of Biotechnology, to Retire As Chairman," Wall Street Journal, December 13, 1996, B12. In addition, at Hybritech, at least, money people and managers made substantive contributions to scientific operations through informed participation in technical decision-making – not only in broad deliberations about research strategies, but also in huddles around lab benches, where, for example, suggestions about experiments were made and discussed. In biotechnology, 'science' and 'business' are hard to tell apart.

developed in recent social studies of science and technology.[100] In this field, the generation and communication of knowledge, the invention and transmission of scientific techniques and practices, and the design and diffusion of technological artifacts have all been adopted as topics of inquiry. In close ethnographic and historical detail, researchers have depicted the construction of technical systems and bodies of scientific knowledge as cultural processes. Facts and artifacts, on this view, are inextricably 'embedded' in social relations and practical traditions of knowing, doing, and speaking in and about the material world. Here, technological progress does not unfold according to any unilinear logic. Studies of tools and techniques in this vein focus on how these things are designed, diffused, and applied always in definite social and historical contexts. And the circumstances in which scientists and technologists work are found to be rife with contingencies that shape bodies of knowledge and the developmental paths of technical systems. As social processes unfold, they open windows of opportunity for particular avenues of scientific and technical advancement, while simultaneously closing others. The specific configurations in which facts and artifacts appear concretely in particular times and places reflect collective human interests and choices that gave rise to them.

---

[100] For recent reviews and older intellectual histories of this field, see H.M. Collins, "The Sociology of Scientific Knowledge: Studies of Contemporary Science," Annual Review of Sociology, 1983, 9: 265-285; Sheila Jasanoff, et al., eds. Handbook of Science and Technology Studies, Thousand Oaks, CA: Sage, 1995; David J. Hess, Science Studies: An Advanced Introduction, New York: New York University Press, 1997; Michael Lynch, "The Demise of the 'Old' Sociology of Science," ch. 2 in Scientific Practice and Ordinary Action: Ethnomethodology and Social Studies of Science, Cambridge University Press, 1993; Steven Shapin, "History of Science and Its Sociological Reconstructions," History of Science, 1982, 20: 157-211; "Here and Everywhere: Sociology of Scientific Knowledge," Annual Review of Sociology, 1995, 21: 289-321; Susan Leigh Star, "Introduction: The Sociology of Science and Technology," Social Problems, 1988, 35: 197-205.

Technologies have social histories. As Bruno Latour puts it memorably: "technology is society made durable."[101]

From this perspective, Donald MacKenzie has suggested that trajectories of technological innovation are usefully conceptualized as self-fulfilling prophecies.[102] "Persistent patterns of technological change," he says, "are persistent in part because technologists and others believe they will be persistent."[103] If people believe in a technology, they will invest in it, dedicate resources to it, and work on it. Technological progress, according to MacKenzie, is conventional in character. It continues as long as people organize their activities in ways that will sustain it (unless, of course, the material world proves unyielding).[104] Working on technologies is a

---

[101] Bruno Latour, "Technology is Society Made Durable," pp. 103-131 in A Sociology of Monsters: Essays on Power, Technology, and Domination, ed. John Law, London: Routledge, 1991.

[102] The original sociological discussion of this concept is found in Robert K. Merton, "The Self-Fulfilling Prophecy," in Social Theory and Social Structure, Glencoe, IL: Free Press of Glencoe, 1949. Merton, however, referred to the false becoming accepted as truth, thus perpetuating "a reign of error."

[103] Donald MacKenzie, "Economic and Sociological Explanations of Technological Change," ch. 3 in Knowing Machines: Essays on Technical Change, Cambridge, MA: MIT Press, 1996, p. 56. The qualifier "in part" is critical. With it, MacKenzie indicates simply that, in matters technological, sometimes nature will not permit human beings to realize their plans.

[104] MacKenzie contrasts his approach with evolutionary theories of innovation in economics, perhaps for the marketing purpose of product differentiation, because evolutionary economics so closely resembles his own view. Evolutionary economists find places in their accounts for social processes and institutions, they subscribe to Herbert Simon's notion of 'bounded rationality,' and they draw, as do sociologists of scientists, from Thomas Kuhn's writings on the centrality of 'paradigms' in technical practice. In order to capture the dynamism of technical and economic change, evolutionary theorists focus attention on the historical path dependence of technological designs. Paul A. David and W. Brian Arthur, for example, explain the course of technological change by locating calculations of economic efficiency in the flow of history and events – the initial success of designs or systems (i.e., adoption in the market) may lead to 'increasing returns' and 'positive feedbacks' to further investments, thus 'locking in' commitments to particular paths of development, and 'locking out' alternatives, even those that may be technically superior. See Paul A. David, "Understanding the Economics of QWERTY: The Necessity of History," pp. 30-49 in Economic History and the Modern Economist, ed. William N. Parker, Oxford: Basil Blackwell, 1986; W. Brian Arthur, "Competing Technologies, Increasing Returns, and Lock-In by Historically Small Events," Economic Journal, 1989, 99: 116-131; and Increasing Returns and Path Dependence in the Economy, Ann Arbor, MI: University of Michigan Press, 1994. Others have developed sociologically oriented variants of this argument. They emphasize

distinctive form of collective activity, but no less social for all of its specialized trade with material objects and processes. Technological innovation involves social organization, the building of institutions. It requires not only the manipulation of material things, but also the management of people and beliefs.[105]

In very general terms, starting and running biotechnology companies, for example, can be said, on this view, to consist in concerted and sustained attempts to make biotechnical prophecies self-fulfilling. To conceptualize innovation in this 'sociocultural' way, Bruno Latour takes to inverting ordinary descriptions of technical success. For example, he substitutes for this representation, "Once the machine works people will be convinced," a dictum that emphasizes the social dimensions of the process, "The machine will work when all the relevant people are convinced."[106] As

---

the social costs of realigning organizations and institutions in order to switch technological gears, and specify roles for organizational structures and routines in leveraging the momentum of "technological paradigms." See, for example, Giovanni Dosi, Technical Change and Industrial Transformation, New York: St. Martin's Press, 1984; Richard Nelson and Sidney Winter, An Evolutionary Theory of Economic Change, Cambridge, MA: Harvard University Press, 1982; and Patrick McGuire, Mark Granovetter, and Michael Schwartz, "Thomas Edison and the Social Construction of the Early Electric Industry in America," pp. 213-246 in Explorations in Economic Sociology, ed. Richard Swedberg, New York: Russell Sage Foundation, 1993. In evolutionary theorizing, however, MacKenzie still finds troublesome residues of technological determinism and hypersociologism. See MacKenzie, Knowing Machines, ch. 3.

[105] See MacKenzie, "Economic and Sociological Explanations of Technological Change," ch. 3 in Knowing Machines. For related discussions, see Henk van den Belt and Arie Rip, "The Nelson-Winter-Dosi Model and Synthetic Dye Chemistry," pp. 135-158 in The Social Construction of Technological Systems: New Directions in the History and Sociology of Technology, eds., Wiebe E. Bijker, Thomas P. Hughes, and Trevor Pinch, Cambridge, MA: MIT Press; and David A. Hounshell, "Hughesian History of Technology and Chandlerian Business History: Parallels, Departures, and Critics," History and Technology, 1995, 12: 205-224.

[106] Bruno Latour, Science in Action: How to Follow Scientists and Engineers Through Society, Cambridge, MA: Harvard University Press, 1987, p. 10. Latour's inversion in this instance lacks a caveat concerning the role of the natural world. To account for the material aspects of technologies, Latour articulates an original metaphysics that rejects common sense appreciations of the relationships between nature and society (and sociological theories that rely on them, as well). For the fullest statement of this philosophy, see Bruno Latour, We Have Never Been Modern, trans. Catherine Porter, Cambridge, MA: Harvard University Press, 1993. Proponents advertise the doctrine as 'amodern.' With this term, they suggest the following: unless people participating in modern Western culture read

the rest of this study will show, this corresponds precisely to biotechnologists' understandings of what they are doing. Industry watchers (and insiders) G. Steven Burrill and Kenneth B. Lee, Jr. describe the typical life course of an entrepreneurial biotech start-up in a way that confirms the interpretations of MacKenzie and Latour:

> In the beginning, there is the "story" – the potential of biological processes to develop products for human health.... Transforming that story into beneficial, competitive products is a matter of building a company that focuses R&D productively, manages clinical trials/field tests and regulatory relations effectively, negotiates supportive partnering and strategic relationships, and – always – maintains access to capital.[107]

Attempts to transform stories of technological possibilities into practical technological realities is what this study is about, and, in a very general sense, what any sociological inquiry into technological innovation must be about. Success (or failure) in hawking an unproven technology depends, at every juncture, on what sociologist Erving Goffman called the arts of 'impression management.'[108] If technologists are to make progress, or pursue their work at all, they must enlist the cooperation of others. In order to receive this aid, they have to generate and sustain faith in their projects.[109] They have to sell their stories effectively. They have to make them believable. Without securing the confidence of others, technologists and their plans go nowhere. The first step in developing a new technology, then, involves

---

the new philosophy, they will not be able to understand fully the significance of things in the world around them.

[107] Steven G. Burrill and Kenneth B. Lee, Jr., Biotech '93: Accelerating Commercialization, An Industry Annual Report, San Francisco, CA: Ernst & Young LLP, 1992, p. 3.

[108] Erving Goffman, The Presentation of Self in Everyday Life, New York: Anchor Books, 1959.

[109] For the views of an industry stock analyst on this point, see Richard A. Bock, "The Importance of 'Hype,'" Biotechnology, 1986, 4: 865-867.

establishing the credibility of one's story. All subsequent steps involve maintaining it. Steven Shapin has argued that in social studies of science and technology: "credibility should not be referred to as a 'fundamental' or 'central' topic – from a pertinent point of view it is the only topic."[110] Shapin is not speaking solely of judgments about facts or technologies, however. He proposes that "knowing about things" always entails "knowing about people."[111] Belief in an untried technology can rest at last only on faith and trust in the persons who speak for it. Cole Owen, a consultant in the biotechnology industry warns entrepreneurs that even if a technology to be developed appears from every indication to be a good one, "you probably can't prove that it will work."[112] For this reason, when evaluating plans for a biotech start-up, seasoned investors begin by evaluating, not reports of scientific facts (the veracity or implications of which they are unlikely to be in a position to judge independently), but rather the people involved.[113]

Bioentrepreneurs commonly set out on their undertakings by soliciting financial support, usually from venture capitalists. In this, they are obliged, if they are to be funded, to make their stories, their business plans, 'look right' on paper, on projection screens, or, as legend often has it, on restaurant napkins, or on the backs of

---

[110] Steven Shapin, "Cordelia's Love: Credibility and the Social Studies of Science," Perspectives on Science, 1995, 3, 3: 255-275; quote on p, 257-258. Shapin refers here specifically to scientific knowledge, but the statement applies just as surely to technological development.

[111] Steven Shapin, A Social History of Truth: Civility and Science in Seventeenth-Century England, Chicago: University of Chicago Press, 1994, ch. 6.

[112] Cole Owen, "How to Start and Manage a High Tech Company," Owen & Associates, Inc., Del Mar, California, 1 April 1996.

[113] Drew Senyei, "Venture Financing," Enterprise Partners, La Jolla, CA, May 1996.

matchbook covers. The kinds of things that have to look right are budgets, financial projections, organizational charts, experimental results, scientific credentials, research schedules, and various other sorts of facts and figures. These things indicate to investors, not so much what is the case in the world, for they are often descriptions of some imagined future, but rather what an individual or group knows about what they are trying to do, what competencies they possess, and what they may be able to accomplish. According to Coopers & Lybrand, L.L.P., a leading business consulting firm, the "three keys" to obtaining venture capital are 1) understanding the process [of venture investing]; 2) writing the business plan [in a way that persuades the reader that the plan is 'doable']; and 3) preparing the financials [which indicate conceptions of the market for the proposed technology or product].[114] Entrepreneurs are urged here to concern themselves with social knowledge, with understandings of what venture capitalists are about, what they typically look for in prospective investments, and what they are likely to consider plausible, realistic proposals or market analyses. They are also advised to present themselves as people who know about such things, and to recognize that personal reputation and character are the vehicles that transport technologies from the imagination to the market. Formulating plans and financial projections that conform to this social knowledge is "the best way to demonstrate the viability and growth potential of the business." This is so because it showcases "the entrepreneur's knowledge of what is needed to meet the company's objectives. The

[114] Coopers & Lybrand, LLP, "Three Keys to Obtaining Venture Capital," 1996.

first reading of a plan is the venture capitalist's initial opportunity to evaluate the individuals who will manage the business."[115]

This is how it begins. But, as Burrill and Lee point out, maintaining the credibility of biotechnologies requires the building of companies and 'doing things right.' This is accomplished by assembling organizations and staffing them with the 'right' people, by recruiting those who possess the requisite knowledge, experience, skills, qualifications, credentials, or reputations. Within such organizations, R&D operations have to be coordinated effectively (or researchers and developers must be allowed to coordinate themselves in productive ways). When a company is young, it sustains belief in its technologies by showing evidence of progress, by reaching technical milestones, making experiments work, delivering positive results in clinical trials, attracting capital in successive rounds of funding, or signing on corporate partners. Accomplishments and deals of this kind serve to 'validate' the technology. At later stages, successfully setting up manufacturing operations, marketing programs, or a sales force may serve to indicate that a payoff is approaching. All of these things demonstrate the continuing promise of a technology in development and, simultaneously, the efficacy of the organization developing it. Along the way, bioentrepreneurs must carefully protect the reputations of their firms and actively promote the projects in which they are engaged. Investors, stock market analysts, scientific collaborators, the FDA, and many others must be continually reassured that companies and their projects remain good bets.

---

[115] Coopers & Lybrand, LLP, "Three Keys to Obtaining Venture Capital," p. 1.

Citing the compulsory organizational and political work that must be done in order to pave the way for technical advances, John Law refers to technologists as "heterogeneous engineers."[116] Technologists integrate both social and technical knowledge into their practices, and they are obliged at every turn to align their technical projects with social interests and the realities of established social arrangements. As MacKenzie notes, there is a sense in which this conceptualization is banal.[117] It certainly isn't news to life science entrepreneurs who must worry, not only about getting experiments to work, but also about getting experimenters to work together, about chasing dollars, maintaining the optimism and satisfaction of investors, monitoring and competing in the marketplace, cultivating relationships with suppliers, collaborators, and corporate partners, complying with government bureaucracies that impose constraints of various sorts, protecting intellectual properties in the courts, dealing with organizational and personnel problems, encouraging positive public perceptions of biotechnologies, and a host of other issues that some might consider 'non-technical.' Biotechnologists understand the 'embeddedness' of technical work in social processes. They know well, for example, that the conduct and interpretation of experiments and clinical trials are shaped at a fundamental level by expressions of political will in the formulation of FDA standards for determining whether or not a candidate drug is safe and effective. This social fact is a source of endless concern for the scientists, regulatory affairs officers, and chief executives of biotechnology

---

[116] John Law, "On the Social Explanation of Technological Change: The Case of Portuguese Maritime Expansion," Technology & Culture, 1987, 28: 227-252.

[117] Donald MacKenzie, "Introduction," ch. 1 in Knowing Machines, p. 13.

companies. The upshot is this: the solving of technical problems always involves the solving of social and organizational problems.[118] The concept of 'heterogeneous engineering' is banal to the extent that biotechnologists themselves recognize that their tasks are at once technical and social. Nevertheless, this way of characterizing actors in technological settings is a sound one, and, in this study, scientific entrepreneurs are aptly described as 'heterogeneous engineers.' And the social elements of the challenges that these persons take on can be as daunting as the complexities of the 'purely' technical problems that they confront.

Cultivating faith in a biotechnology is a massive undertaking. According to recent estimates, the process of drug discovery, development, and testing, the obstacle course that leads a new compound or treatment from the laboratory to the pharmacy takes on average 12 years and costs somewhere in the neighborhood of $350 million for a single therapeutic product.[119] Obviously, if bioentrepreneurs are to realize their plans, they are required to solicit a staggering measure of good will, and to beg patience over extended periods as they attempt to prove that they and their organizations can, in fact, do what they say they can. Biotechnology companies burn through millions of dollars a year and the large majority have no product revenues to

---

[118] Here, I paraphrase, and transpose to the domain of technology, Shapin and Schaffer's view on the advancement of scientific knowledge: "Solutions to the problem of knowledge are solutions to the problem of social order." See Steven Shapin and Simon Schaffer, Leviathan and the Air Pump: Hobbes, Boyle, and the Experimental Life, Princeton, NJ: Princeton University Press, 1985, p. 332.

[119] U.S. Congress, Office of Technology Assessment, Pharmaceutical R&D: Costs, Risks, and Rewards, Washington, D.C.: Government Printing Office, 1993.

show for it.[120] And investors are not the only persons who receive promissory notes. David Hale, a biotech CEO remarks: "People don't realize the tremendous amount of energy it takes to build a business. You tell your kids and friends, 'I'll see you in a few years.'"[121] Some observers wonder whether biotechnologies have warranted the enormous expenditures of time and money that have been devoted to their development. Robert Teitelman, for example, has referred to the surge of investment enjoyed by the biotech industry in the early 1980s as "biomania."[122] Citing the difficulties that fledgling companies have confronted in managing the process of pharmaceutical product development, Teitelman concludes that the emergence of commercial biotechnology has consisted mostly in greedy professors and venture capitalists taking Wall Street and the public for a premature ride. Because biotechnologies have not enabled rascal start-ups to restructure the ethical drug industry by displacing the huge, well-entrenched pharmaceutical houses that dominate it, he considers commercial biotechnology a "failed revolution."[123] Whether this view is sober, sour, or something else is difficult to judge. Certainly, early expectations for progress in the field were overly optimistic. Still, Teitelman presents a somewhat distorted view of science and technology. He assumes that if biotechnologies had

---

[120] In 1995, the net loss of the average biotechnology company was $726,000 per month. Kenneth B. Lee, Jr., and G. Steven Burrill, Biotech '96: Pursuing Sustainability, Palo Alto, CA: Ernst & Young, LLP, 1995, p. 15.

[121] Tom Gorman, "The Faces Behind Biotech," Los Angeles Times, 27 May 1991, B6.

[122] Robert Teitelman, Gene Dreams: Academia, Wall Street and the Rise of Biotechnology, New York: Basic Books, 1989.

[123] Robert Teitelman, Profits of Science: The American Marriage of Business and Technology, New York: Basic Books, 1994, ch. 19.

really been all that they were cracked up to be, they could somehow have spoken for themselves and, like magnets, attracted appropriate capital investments with no need for marketing or 'hype.' But no unproven science or technology can advance if people don't believe in it, and no method of forecasting or calculation can obviate the need for champions and leaps of faith.[124] In any case, the fact that biotechnology companies have been slow to deliver the technical goods makes their social accomplishments all the more astonishing.

This phenomenon can be read as an invitation to social scientists to investigate the practical social and organizational efforts that biotechnologists have engaged in order to generate and sustain belief in what they do, despite the high costs and lethargic returns that all watching the field now admit have been disappointing. For all the excitement, concern, loyalty, and skepticism that have been inspired or aroused by new ventures in this field, however, surprisingly little has been written about the substance of scientific entrepreneurship. The empirical goal of this work is to document the ways in which biotechnologists have told credible stories and built organizations in San Diego in order to accomplish their entrepreneurial ends and make biotechnical prophecies self-fulfilling. It focuses on the practical work undertaken by these individuals as they founded new firms and established research and development operations within them. The role of 'bioscience entrepreneur' in the life sciences and the pharmaceutical industry is a relatively new one, just over twenty-five years old,

---

[124] For arguments, see Richard A. Bock, "The Importance of 'Hype,'" Bio/Technology, 1986, 4: 865-867; Bruno Latour, Aramis, or The Love of Technology, trans. Catherine Porter, Cambridge, MA: Harvard University Press, 1996; Modesto A. Maidique, "Entrepreneurs, Champions, and Technological Innovation," Sloan Management Review, 1980, Winter: 59-76; and Donald Schön, "Champions for Radical New Inventions," Harvard Business Review, 1963, 41: 77-86.

and it continues to evolve. Examining the activities and obligations that this social role encompasses and interpreting it as a form of 'heterogenous engineering' can shed light on the sociological dimensions of the biotechnology phenomenon.

THE CIRCULATION AND CONCENTRATION OF KNOWLEDGE AND SKILL

Social studies of science and technology provide additional conceptual resources that can be applied to this end. Empirical inquiries in this area attend to the concrete, contextual aspects of scientific and technological practice. Stressing the local and the particular, researchers in this field investigate the ways in which tools are fashioned and facts are generated by particular actors in specific times and places, and, naturally, they have favored ethnographic and historical methods. They have taken up the empirical task of describing the ways in which people construct and employ scientific and technical methods in the course of ordinary practical activity. The aim is a 'microsociological' understanding of how scientific practices and routines are interactively shaped, and how uses of instruments and interpretations of technical standards are adapted to solve problems in various settings and circumstances. In the past twenty-five years, numerous case studies conducted for this purpose have yielded unique 'naturalistic' appreciations of science and technology as cultural forms. These inquiries have addressed a broad range of topics, but of special significance for this study are two: the nature of technical skill, and the processes by which such know-how is transferred and diffused.

By devoting attention to the mundane, routine aspects of experiment and laboratory life – the handling of materials, the construction and use of instruments, the

interpretation of data, the writing up of findings, and so on – ethnographic investigations of scientific and technological work have revealed messy, uncertain processes of trial and error that hardly resemble the straightforward application of rationalized methods and procedures. The work of Harry Collins has been particularly influential in this regard.[125] His reports depict scientific and technical sense-making, the transmission of scientific and technical skills, and the production and communication of new knowledge and capabilities as context-specific activities that depend crucially on processes of enculturation – teaching by ostension and learning by doing. The technical know-how required to construct instruments, to generate replicable experimental data, and to establish matters of fact is said to reside in 'embodied' tacit understandings.[126] These understandings defy comprehensive formalization. Scientific and technological competence, so these studies suggest, is expressed in artful craftwork characterized by peculiar abilities – a singular sense of judgment, an inarticulable 'feel' for a phenomenon or a technique, or a knack for

---

[125] See, for example, H.M. Collins, Changing Order: Replication and Induction in Scientific Practice, Chicago: University of Chicago Press, 1992 [1985]. Collins' interpretive mode of sociological inquiry was influenced significantly by Peter Winch's neo-Weberian philosophy of social science. See Peter Winch, The Idea of a Social Science and Its Relation to Philosophy, Atlantic Highlands, NJ: Humanities Press, 1990 [1958]. Collins' view of tacit know-how as a fundamental element of experimental practice draws substantially on Michael Polanyi's articulation of the concept. See Michael Polanyi, Personal Knowledge: Towards a Post-Critical Philosophy, Chicago: University of Chicago Press, 1958. Collins' early empirical works were groundbreaking first steps in a broad trend in science studies toward the ethnographic study of experiment and laboratory practice. For examples, see Bruno Latour and Steve Woolgar, Laboratory Life: The Construction of Scientific Facts, Princeton, NJ: Princeton University Press, 1986 [1979]; Karin Knorr-Cetina, The Manufacture of Knowledge: An Essay on the Constructivist and Contextual Nature of Science, Oxford: Pergamon, 1981; and Michael Lynch, Art and Artifact in Laboratory Science: A Study of Shop Talk and Shop Work in a Research Laboratory, London: Routledge & Kegan Paul, 1985.

[126] H.M. Collins, "The TEA Set: Tacit Knowledge and Scientific Networks," Science Studies, 1974, 4: 165-186; "The Seven Sexes: A Study in the Sociology of a Phenomenon, or Replication of an Experiment in Physics," Sociology, 1975, 9: 205-224; and "The Son of Seven Sexes: The Social Destruction of a Physical Phenomenon," Social Studies of Science, 1981, 11: 131-158.

getting experiments to work.[127] These skills are not rule-bound. They cannot be systematized. They can be acquired only through practical experience and personal interaction with others who can show the way. The social foundations that support the production of new knowledge in scientific and technological fields are located in private networks of exchange – elite "core sets" that maintain essential cognitive and social resources within their restricted circles.[128] As well as providing empirical illustrations of how the sciences work and progress in particular instances, these findings also make a more general point: they demonstrate that full understandings of invention, innovation, and technology transfer can be obtained only by examining concrete, situated interactions and relations among particular individuals and groups engaged in these activities.

Now that laboratory ethnographers have established that science-in-the-making is coextensive with society-in-the-making, and that technical know-how is inescapably situated and context-bound,[129] a pressing concern for researchers in this field is to account for the ways in which knowledges and technologies 'travel,' i.e., how they come to be widely accepted and utilized beyond the local contexts in which they are

---

[127] Scientists themselves often talk about their work in these terms. Molecular biologist Barbara McClintock, for example, famously described the substance and end of her research as "a feeling for the organism." See Evelyn Fox Keller, A Feeling for the Organism: The Life and Work of Barbara McClintlock, San Francisco, CA: W.H. Freeman, 1983.

[128] H.M. Collins, "The Role of the Core-Set in Modern Science: Social Contingency with Methodological Propriety in Science," History of Science, 1981, 19: 6-19; G.D.L. Travis and H.M. Collins, "New Light on Old Boys: Cognitive and Institutional Particularism in the Peer Review System," Science, Technology & Human Values, 1991, 16: 322-341.

[129] See Adi Ophir and Steven Shapin, "The Place of Knowledge: A Methodological Survey," Science in Context, 1991, 4: 3-21.

generated.[130] Consequently, the topics of communication among scientists and the transmission of experimental techniques and practices have received increasing attention from sociologists of science and technology. The objective is to account for the massive success that the sciences have enjoyed as social institutions, and as forces that continue to transform the modern world – without assuming that the practical merits and applications of scientific knowledge, techniques, or products are self-evident to those who might be persuaded to adopt them. In response to this problem, researchers have interpreted the advance of scientific facts and artifacts as the extension of social networks in which scientific values, practices, and forms of action become established.[131] Diffusions of knowledge, tools and techniques are said to reflect outcomes of social interactions within dense webs of communication and exchange. They are shaped, and facilitated or impeded by competition and the concentration of power,[132] the negotiation and coordination of meanings, definitions of situations, and practical agendas,[133] and teaching and learning done by particular

---

[130] Steven Shapin, "Here and Everywhere: Sociology of Scientific Knowledge," Annual Review of Sociology, 1995, 21: 289-321; p. 304-309.

[131] Michel Callon, John Law, and Arie Rip, eds., Mapping the Dynamics of Science and Technology: Sociology of Science in the Real World, London: Macmillan, 1986; Bruno Latour, Science in Action: How to Follow Scientists and Engineers Through Society, Cambridge, MA: Harvard University Press, 1987; "Give Me a Laboratory and I Will Raise the World," pp. 141-170 in Science Observed: Perspectives on the Social Study of Science, eds., Michael Mulkay and Karin Knorr-Cetina, London: Sage, 1982; Joseph O'Connell, "Metrology: The Creation of Universality by the Circulation of Particulars," Social Studies of Science, 1993, 23: 129-173.

[132] Bruno Latour, The Pasteurization of France, trans. Alan Sheridan and John Law, Cambridge, MA: Harvard University Press, 1988.

[133] Wiebe E. Bijker, Of Bicycles, Bakelites, and Bulbs: Toward a Theory of Sociotechnical Change, Cambridge, MA: MIT Press, 1997; Adele E. Clarke and Elihu Gerson, "Symbolic Interactionism in Social Studies of Science," pp. 179-214 in Symbolic Interaction and Cultural Studies, ed. Howard S. Becker and Michael M. McCall, Chicago: University of Chicago Press, 1990; Joan H. Fujimura, "Crafting Science: Standardized Packages, Boundary Objects, and 'Translation,'" pp. 168-214 in Science as Practice and Culture, ed., Andrew Pickering, Chicago: University of Chicago Press, 1992.

persons in face-to-face contact.[134] In general terms, the conventional wisdom in the field now holds that sciences and technologies succeed where they can be assimilated in local cultures and employed to solve practical problems of social and technical order in these settings. On this pragmatic view, the diffusion of scientific and technical practices depends largely on negotiations of interest, meaning, and value among individuals and groups.

GEOGRAPHY AND ENTREPRENEURSHIP

This general approach is well suited for investigating entrepreneurship and innovation in the biotechnology industry, and it need not be restricted to narrowly scientific or technical aspects of these phenomena. It is applicable to any form of knowledge or action, and to all of the disparate varieties of expertise that biotech companies utilize. Growth in high-tech, post-industrial economic sectors depends crucially on the drawing together of information, knowledge, and skill (in matters technical, organizational, political, and so on). Much of the work done by high-tech entrepreneurs is devoted to the acquisition and coordination of these resources. In order to innovate and remain competitive, entrepreneurial high-tech ventures must secure access to and effectively organize many different forms of specialized scientific, technical, financial, legal, managerial, and operational know-how. Recent social studies of science and technology provide ethnographic and historiographic

---

[134] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995, ch. 2-3; H.M. Collins, "The Scientist in the Network: A Sociological Resolution of the Problem of Inductive Inference," ch. 6 in Changing Order: Replication and Induction in Scientific Practice, Chicago: University of Chicago Press, 1992 [1985].

exemplars for rendering sociologically the substance of this kind of activity.[135] The emergence in San Diego of a 'local biotechnology-generation complex' can be understood as the creation, maintenance, and extension of social relationships through which, and in which, knowledge, the lifeblood of the industry, is diffused and applied. The technological and organizational innovations that have characterized the formation of this entrepreneurial milieu can be attributed to the actions of individuals working together, distributing, recombining, and utilizing critical resources in the course of establishing and maintaining localized networks of communication and exchange.[136]

The theoretical approach outlined above permits the incorporation of both time and place into causal sociological accounts, making them concrete. Recent social studies of scientific knowledge have stressed the analytic centrality of location and process in examinations of material scientific practices. So far, however, most research on the commercialization of biological knowledge in this field has focused more or less narrowly on the laboratory, or on regulatory governance processes; few researchers in this area have ventured into corporate boardrooms.[137] The phenomenon

---

[135] For a similar analysis offered by students of business, management, and organizations, see John Seely Brown and Paul Duguid, The Social Life of Information, Boston, MA: Harvard Business School Press, 2000. Using examples involving the incorporation of electronics, computer networking, and telecommunications into organizational life, Brown and Duguid describe how knowledge is dispersed, and innovation thereby facilitated, within "communities of practice."

[136] The localization is social and not necessarily geographic.

[137] The works of anthropologist Paul Rabinow are notable exceptions. See Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press, 1996; French DNA: Trouble in Purgatory, Chicago: University of Chicago Press, 1999; and Paul Rabinow and Talia Dan-Cohen, A Machine to Make a Future: Biotech Chronicles, Princeton, NJ: Princeton University Press, 2004. Of course, access to such sites is often a problem for social researchers 'studying up,' i.e., investigating the activities of those with greater social status.

of scientific entrepreneurship, as a result, has not been subjected to much close scrutiny. The same is generally true in other fields of research that concern themselves with technological innovation. Economic geographers, for example, have mapped industrial and technological development activities onto topographic and social landscapes, but they have devoted little ethnographic attention to the face-to-face interactions and decision-making processes in which contingent courses of technological innovation, organizational change, and economic growth are shaped.[138]

The geographers have lately produced rich literatures that examine the social and economic dynamics of science parks, high-tech 'incubators,' 'technopoles,' and 'technoregions' from a variety of modern and postmodern theoretical perspectives. Some identify and chart the social and geographic boundaries of economic factors, institutional structures, and other 'ingredients' that contribute to regional innovation.[139] Many attempt to account for 'R&D spillovers' (non-market knowledge transactions) and spatial concentrations or 'agglomerations' of resources by tracking information flows across institutions, organizations, and physical distances.[140] Others

---

[138] Many economic geographers stress the importance of technical knowledge to industrial innovation, and they discuss its tacit, embodied character. Still, they rarely provide substantive descriptions of the ways in which this knowledge is cultivated and transmitted.

[139] Paul A. David and Joshua Rosenbloom, "Marshallian Factor Market Externalities and the Dynamics of Industrial Location," Journal of Urban Economics, 1990, 28: 349-370; Maryann P. Feldman, The Geography of Innovation, Boston: Kluwer Academic Press, 1994; Amy K. Glasmeier, "Factors Governing the Development of High-Tech Industry Agglomerations: A Tale of Three Cities," Regional Studies, 1988, 22: 287-301; Ann R. Markusen, Peter G. Hall, and Amy K. Glasmeier, High Tech America: The What, How, Where, and Why of the Sunrise Industries, Boston: Allen & Unwin, 1986; C.S.P. Monck, et al., Science Parks and the Growth of High Technology Firms, London: Croom Helm, 1988.

[140] David B. Audretsch and Paula E. Stephan, "Company-Scientist Locational Links: The Case of Biotechnology," American Economic Review, 1996, 86: 641-652; Zvi Griliches, "The Search for R&D Spillovers," Scandinavian Journal of Economics, 1992, 94 (suppl.): 29-47; Walter W. Powell, Kenneth W. Koput, James I. Bowie, and Laurel Smith-Doerr, "The Spatial Clustering of Science and Capital:

are attentive to the global character and impact of regional development, and to the compression of distances and event durations in post-industrial knowledge and information economies. Studies of this kind treat localized processes of high-tech innovation within broader historical processes, charting the accumulation and dispersion of capital, labor, and materials across vast stretches of time and space. They seek to interpret or explain, in a number of different ways, how complex, interrelated economic and social logics have given rise, following global transformations in post-World War II structures of competition, to industrial expansion and decline in particular regions, and forms of post-industrial revitalization in others.[141]

However, while economic geographers have addressed the spatial and temporal dimensions of high-tech innovation, their explanations are typically framed at high levels of abstraction. They remain descriptively thin, and generally exclude

---

Accounting for Biotech Firm-Venture Capital Relationships," Regional Studies 2002, 36, 3: 291-305; Lynne G. Zucker, Michael R. Darby, and Jeff Armstrong, "Intellectual Capital and the Firm: The Technology of Geographically Localized Knowledge Spillovers," Working Paper No. 4946, Cambridge, MA: National Bureau of Economic Research, 1994. Studies of this kind attempt to establish paper trails that indicate formal and informal information sourcing. The typical measures on which inferences are based include formal commercial affiliations of university-based scientists and patterns of authorship and citation in patents and scientific publications. On the use of patents, see Zvi Griliches, "Patent Statistics as Economic Indicators," Journal of Economic Literature, 1990, 28: 1661-1707; Adam Jaffe, Manual Trajtenberg, and Rebecca Henderson, "Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations," Quarterly Journal of Economics, 1993, 108: 577-598; cf. Ajay Agrawal and Rebecca Henderson, "Putting Patents in Context: Exploring Knowledge Transfer from MIT," Management Science, 2002, 48, 1: 44-60; Joan O.C. Hamilton, "Commentary: Measuring Biotech by Patents is Patently Absurd," Business Week, 1996, April 22: 47.

[141] See, for example, Manuel Castells, ed., High-Technology, Space, and Society, Beverly Hills, CA: Sage, 1985; Peter G. Hall and Ann R. Markusen, eds., Silicon Landscapes, Boston: Allen & Unwin, 1986; Frank Moulaert and Allen J. Scott, Cities, Enterprises, and Society on the Eve of the 21st Century, London: Pinter, 1997; Allen J. Scott, New Industrial Spaces: Flexible Production, Organization, and Regional Development in North America and Western Europe, London: Pion, 1988; Michael Storper and Allen J. Scott, eds., Pathways to Industrialization and Regional Development, London: Routledge, 1992.

the points of view of actors involved in processes of high-tech industrial development. The causal significance of 'micro-level' interactions is largely discounted.[142] In this study, I assume that knowledge of situated social actions at specific historical moments is critical when the topic of inquiry is a process as complex, dynamic, and uncertain as the emergence in real time of an industry characterized by high technologies and new organizational forms. In addition, economic geographers have largely ignored the grounded meanings of things in high-tech settings. The meanings to which they attend are typically those associated with positions in theoretical and ideological debates. In this study, I assume that gaining familiarity with the in situ meanings of high-tech activities, relationships, and objects is indispensable for understanding the ways in which things like incubators, technopoles, fresh markets, and novel organizational forms take shape in the world.

Business scholars Howard E. Aldrich and C. Marlene Fiol maintain that the creation of meaning is a central feature of industrial and organizational innovation. They advise researchers investigating this phenomenon to pay special attention to the ways in which entrepreneurs attempt to establish and maintain cognitive and sociopolitical legitimacy for their projects. Aldrich and Fiol assert that "the social construction of organizational reality involved in building a new industry requires meaning making on a grand scale."[143] Economic geographers often overlook what processes of high-tech development mean to high-tech people, and they often attach to

---

[142] There are rare exceptions. See, for example, Edward J. Malecki, "What About People in High Technology? Some Research and Policy Considerations," Growth and Change 1989, (Winter): 67-79.

[143] Howard E. Aldrich and C. Marlene Fiol, "Fools Rush In? The Institutional Context of Industry Creation," Academy of Management Review, 1994, 19: 645-670; p. 666.

these processes alternative theoretical meanings that actors themselves do not recognize. This is fine. Their works represent interpretations from legitimate points of view, but there is a price to be paid for discounting what people think and say about what they are doing. When abstract models of action are substituted for actual beliefs, motives, or justifications, the complexities of the social process are lost, and there is a tendency to treat departures from conventional patterns of action as instances of deviance or, as is common in economic geography, of capital tugging people along in its wake.[144]

The analytic strategy laid out in the previous section is designed to be attentive to situated actions and contextual meanings, and to treat them as fundamental to the geographic travel and clustering of knowledge, materials, and people in time and space. In this way, it is reminiscent of Chicago School sociology, and in particular, Robert Park's ecological community studies. The tradition established by Park and his students and colleagues at Chicago fell long ago by the disciplinary wayside, but, as Andrew Abbott has argued, the time may be ripe for reviving it.[145] Although the technopoles of Southern California and other centers of 'flexible accumulation' and 'time-space compression' may seem light years way from the old neighborhoods and ethnic enclaves of the Windy City, for students of the post-industrial knowledge society, the theoretical and methodological foundations of the Chicago school

---

[144] Entrepreneurial innovations are sometimes characterized as deviant because they represent disruptions in established orders. Such characterizations rest, at bottom, on the foundations of an essentialist social philosophy in which objective rules necessarily precede and always account for appearances of social order and instances of normatively sanctioned behavior.

[145] Andrew Abbott, "Of Time and Space: The Contemporary Relevance of the Chicago School," Social Forces, 1997, 75, 4: 1149-1182; see also, David R. Maines, "Narrative's Moment and Sociology's Phenomena: Toward a Narrative Sociology," Sociological Quarterly, 1993, 34, 1: 17-38.

comprise a viable sociological model for addressing questions of geography and culture in high-tech development.[146]

In developing the Chicago school approach, Park drew substantially from the social theory of his teacher, Georg Simmel. Simmel's thinking has been described as "speculations on a social geometry, on the importance of distance and position within social space."[147] Simmel maintained that the formal measurement and analysis of social geographies was distinct and separable from social philosophy, the province of subjectivity and meaning,[148] but Park combined them, always noting the fundamental interrelatedness of social geometries and the collective 'definitions of situations' that coalesce within them.[149] Park wrote social histories of communities and institutions that emphasized the importance of physical location in processes of communication, the creation and maintenance of group solidarity, and organizational form and change.

---

[146] Robert E. Park, Human Communities: The City and Human Ecology. The Collected Papers of Robert Ezra Park, Vol. II, eds. Everett C. Hughes, Charles S. Johnson, Kitsuichi Masuoka, Robert Redfield, and Louis Werth. Glencoe, IL: The Free Press, 1952.

[147] Fred H. Matthews, Quest for an American Sociology: Robert E. Park and the Chicago School, Montreal: McGill-Queens University Press, 1977, p. 41.

[148] See Georg Simmel, Conflict & The Web of Group-Affiliations, trans. Kurt H. Wolff and Reinhard Bendix, New York: The Free Press, 1955. Recent sociological works that conceptualize and represent organizations, interlocking directorates, and cross-institutional communications and collaborations as networks are basically Simmelian, although participants in the field rarely invoke Simmel as a theoretical progenitor. They are accustomed to portraying social network mapping as, instead, a novel convergence of sociology with contemporary streams of thought in mathematics and physics on complexity and the emergent properties of various kind of phenomena. See, for example, Philip Ball, Critical Mass: How One Thing Leads to Another, Farrar, Straus, and Giroux, 2004; Duncan J. Watts, Small Worlds: The Dynamics of Networks between Order and Randomness, Princeton: Princeton University Press, 1999; Duncan J. Watts, Six Degrees: The Science of a Connected Age, New York: W.W. Norton & Company, 2003.

[149] See Robert E. Park, "The Concept of Position in Sociology," Publications of the American Sociological Society, 1926, 20: 1-14. W.I. Thomas' famous dictum "If men define situations as real, they are real in their consequences" appears in W.I. Thomas and Dorothy Swaine Thomas, The Child in America: Behavior Problems and Programs, New York: Knopf, 1928; p. 572.

This dissertation can be construed as a similar kind of analysis, an inquiry into the sociocultural processes that have given places called Torrey Pines Mesa and the Sorrento Valley their contemporary meanings for residents of San Diego. These are the precincts of the city that surround the Scripps Research Institute, the Salk Institute of Biological Studies, and the University of California, San Diego. They are also the locales in which the city's new biotechnology companies have taken up residence. To follow individual careers in this place is to track the formation of an entrepreneurial culture, a social space in which people develop and disseminate the know-how required to make technological and organizational innovations. This 'methodology' affords opportunities for developing rich understandings of bioscientific entrepreneurship.

III. THEORIES OF ENTREPRENEURSHIP

'Know thyself' is a good saying, but not in all situations. In many, it is better to say 'Know others.'

Menander

A CONFOUNDING TOPIC

Entrepreneurship has always confounded academic analysts. In an attempt to formulate a broadly acceptable definition of the phenomenon, sociologist Brigitte Berger calls it "an innovative and value-adding economic activity."[1] Beyond vague statements of this kind, which are unobjectionable, there is little agreement among social scientists about how entrepreneurship is properly identified, described, classified, or explained. Students of commercial and industrial innovation have drafted many different theories to account for the phenomenon. Most are generalizing. They are formulated in order to clarify the boundaries of entrepreneurship as a concept and a category. They attempt to specify common exemplifying features found across the entire range of activities conventionally classed as entrepreneurial, and so provide criteria for distinguishing entrepreneurial acts from other kinds. Unfortunately, there is little conceptual unity among these interpretations. Many of them incorporate assumptions and claims that contradict the rudimentary principles of others.

Because there is no consensus among social scientists regarding how properly to understand entrepreneurship in theory or practice, and because so little headway has

[1] Brigitte Berger, "Introduction," pp. 1-12 in The Culture of Entrepreneurship, ed. Brigitte Berger, San Francisco, CA: ICS Press, 1991; p. 8.

been made toward a generalizing explanation, the idea of disregarding past and current academic theories of entrepreneurship altogether is a tempting one. Nevertheless, in this chapter, I discuss the principal strands of theorizing on the topic in the disciplines of economics, history, psychology, anthropology, and sociology. I wrap up this survey by relating the conceptual foundations of economist Don Lavoie's interdisciplinary and hermeneutic approach to understanding entrepreneurship.[2] Contemporary students of entrepreneurship in the social sciences have largely neglected hermeneutic theory (along with empirical research on the interactive dimensions of culture and knowing). Lavoie's writings have been almost completely ignored, so far as I can tell, but I have found them useful for this analysis nonetheless.[3] They dovetail seamlessly with the Chicago School approach to the study of communities, Howard Becker's pragmatic understanding of culture, and the leading theoretical orientations in contemporary social studies of scientific practice and scientific culture outlined in the previous chapter. Lavoie urges students of entrepreneurship to focus on the collective practices that define specific social,

---

[2] Don Lavoie, "The Discovery and Interpretation of Profit Opportunities," pp. 33-51 in The Culture of Entrepreneurship, ed. Brigitte Berger, San Francisco, CA: ICS Press, 1991. See also Lavoie, Don, ed., Economics and Hermeneutics, London: Routledge, 1990; and Don Lavoie and Emily Chamlee-Wright, eds., Culture and Enterprise: The Development, Representation, and Morality of Business, London: Routledge, 2000.

[3] Lavoie's writings on entrepreneurship are 'metatheoretical' rather than substantive. They are abstract ideas about the definition and conceptualization of economic knowledge and activity, and human nature generally, and so belong to the philosophy of economics. Once committed to particular substantive theories, methods of inquiry, conventions of speech, and established institutional processes, social scientists (like natural scientists) typically suspend consideration of metatheoretical assumptions, at least insofar as empirical research in their professional specialties is concerned. For academics who cast their lots with established theoretical 'schools of thought,' there are few incentives (and many possible penalties) for entertaining philosophical ideas contrary to those espoused by authoritative members. Among academic groups that conduct empirical studies of entrepreneurship, the market for philosophical writings is limited.

cultural, and historical settings (i.e., the concrete social preconditions of entrepreneurship), and on the substance and meaning of entrepreneurial actions and ideas in relation to them. In this dissertation, I adopt Lavoie's analytical scheme as a guide for writing a theoretically informed history of entrepreneurship in San Diego's life science and biotech community.

Although entrepreneurship is notoriously difficult to define with precision, it is safe to say that it consists in the coordination and utilization of available resources to create new objects, processes, or services of estimable value. It is safe, too, I hope, to assert that none of these resources (materials, capital, ideas, people) can be counted as factors contributing to social or technical change until entrepreneurs assemble and make use of them. If this is accepted, then processes of innovation plainly begin with entrepreneurial actions. At any given point in history, conditions may be more or less ripe for the arrival or application of some new technological phenomenon. The accomplished fact of a new tool or a new technique of production, however, is not something that can be read prospectively. Entrepreneurs are required to bridge the gap between a past that is not fully cognizant of its possibilities, and a future in which some of these possibilities become widely recognized and actively pursued. In the case of biotechnology, the fact that certain scientific discoveries made in the 1970s could be commercialized and eventually form the basis of a new industrial sector was not readily apparent until entrepreneurs began to demonstrate to others how it might be accomplished, and to convince them that biotechnologies could generate new medicines for physicians and significant profits for investors. In biotechnology, the capacity to translate suggestive results of laboratory experiments into useful

pharmacological products and economic expansion has been generated by entrepreneurial actions.

CLASSICAL AND ALTERNATIVE CONCEPTIONS OF ENTREPRENEURSHIP

Ironically, while the term entrepreneurship is usually invoked to refer to a profit-oriented economic activity, the discipline of economics has had relatively little to say about it. When economic theorists have addressed the topic, they have typically asked 'what is the economic function of the entrepreneur?' And they have generally agreed on a broad answer: an entrepreneur is an economic agent who spies profit opportunities and moves to take advantage of them. In capitalist economies, the entrepreneur's function is to spur economic progress. However, in the dominant classical equilibrium model of the economic process, there is nothing that distinguishes entrepreneurial action from any other informed, rational economic behavior based on calculations of expected utility. The classical model is static. Within it, all actors are assumed to possess the knowledge necessary to arrive at rational expectations. There are no means in this scheme for crediting or blaming individual actors for innovation and change. In classical economics, entrepreneurship is a form of utility maximizing and is fully explained by the systemic pull of profit opportunities. Only when the basic assumptions of the classical model are relaxed can entrepreneurship be conceptualized as a distinct form of economic activity, one that is creative rather than systematically rational.

In the modern history of economics, a few voices from the wilderness have piped up with alternatives to the disciplinary status quo. These efforts have been

partially successful in terms of opening up conceptual spaces in which to treat entrepreneurship as a form of economic action distinct in certain respects from others. For example, in 1921, Frank Knight published an unorthodox book that abandoned the familiar classical presuppositions of perfect information and perfect competition.[4] This move allowed him to distinguish uncertainty from calculable economic hazards, and to equate the entrepreneurial function with the assumption of undetermined and uninsurable risks. The substance of economic enterprise, in Knight's view, involves acting in the face of unknown and unforeseeable market conditions. In real life economic activity, investments are made without guarantees concerning outcomes. Individuals who gamble with their capital must be able to tolerate conditions of uncertainty, and it is for this tolerance that the successful businessperson may be rewarded with profit. With this conceptualization, Knight managed to separate entrepreneurship from utility maximizing.

Still, in Knight's abstract analysis, entrepreneurship remains strictly a chase after financial gain. There is little mention of the organizational work that entrepreneurs are obliged to undertake and there is no categorical distinction to be made between innovative and routine profiteering. Further, most analysts today, following Joseph Schumpeter, agree that the assumption of financial risk is incidental to entrepreneurial practice. Schumpeter proposed that in the analysis of entrepreneurship, "risk bearing should not be described as an essential or defining function...for it is obviously the capitalist who bears the risk and who loses his money

[4] Frank Knight, Risk, Uncertainty, and Profit, Boston, MA: Houghton Mifflin, 1921.

in case of failure."[5] Entrepreneurs take chances on failure, disappointment, loss of reputation, etc., and they sometimes take chances on personal financial ruin, but most entrepreneurial projects imperil 'OPM' – other people's money. Certainly, this is true in the field of biotechnology where the sums of money required for product development are enormous. Entrepreneurial life scientists and research managers cannot personally finance their projects. In the commercialization of biotechnologies, venture capitalists and other public and private investors assume the financial risks.

Another notable challenge to the basic assumptions of classical economic theory was posed in the first half of the 20th century by the 'subjectivism' of the Austrian School economists.[6] The Austrians rejected the classical idea that economic action consists in choices made within objective opportunity structures. The subjectivist view holds that the sense and meaning of an economic action cannot be properly understood without taking into account the (situated and limited) knowledge, expectations, and plans of the individual actor. Starting from this basic presupposition, school member Israel Kirzner conceptualized entrepreneurship as 'market discovery.'[7] In his analysis, the defining feature of entrepreneurial action is alertness. The entrepreneur is someone who recognizes profit opportunities (i.e.,

---

[5] Joseph A. Schumpeter, "Economic Theory and Entrepreneurial History," ch. 21 in Essays: On Entrepreneurs, Innovations, Business Cycles, and the Evolution of Capitalism, ed. Richard V. Clemence, New Brunswick, NJ: Transaction, 1989.

[6] See Freidrich von Hayek, Individualism and Economic Order, Chicago: University of Chicago Press, 1948; Ludwig von Mises, Human Action: A Treatise on Economics, London: William Hodge, 1949.

[7] Israel M. Kirzner, Competition and Entrepreneurship, Chicago: University of Chicago Press, 1973; Perception, Opportunity, and Profit: Studies in the Theory of Entrepreneurship, Chicago: University of Chicago Press, 1979; Israel M. Kirzner, et al., eds., The Prime Mover of Progress: The Entrepreneur in Capitalism and Socialism, London: The Institute of Economic Affairs, 1980.

market inefficiencies or unsatisfied needs) when others do not. Entrepreneurs move first to engage in arbitrage, improve production, or supply unmet demands. They receive supernormal returns for their alertness and initiative until other producers begin to follow their lead and saturate the market that the entrepreneurs have opened up or reformed. The role of the entrepreneur, then, for Kirzner, is to move economies back toward states of equilibrium. Kirzner's theory of entrepreneurship remained bound by the traditional commitments of economists to methodological individualism and equilibrium analysis. Still, like Knight, he was able to portray entrepreneurship as a form of judgment rather than objective calculation.

Neither Knight nor Kirzner were inclined to speculate on or investigate the emergence of entrepreneurial ventures or values. For both, the lure of profits was taken for granted as the motive force behind entrepreneurial activity, and beyond this, both were content to leave the 'formation' of entrepreneurs and entrepreneurship to researchers in other fields. Perhaps unique among prominent economists in exploring substantive theoretical ideas about the 'non-economic' sources of economic enterprise was Schumpeter. In a review of sociological research on entrepreneurship, Alberto Martinelli calls Schumpeter "the theorist of entrepreneurship par excellence."[8] In Schumpeter's theory, entrepreneurship is a dynamic force. It disrupts established patterns of economic activity. Schumpeter's entrepreneurs assemble novel recombinations of economic resources or factors of production in order to create new

[8] Alberto Martinelli, "Entrepreneurship and Management," pp. 476-503 in The Handbook of Economic Sociology, ed. Neil J. Smelser and Richard Swedberg, Princeton, NJ: Russell Sage Foundation, 1994; p. 478.

things of value.[9] They mobilize and organize people, materials, and bodies of proprietary knowledge in innovative ways. But Schumpeter stressed that these resources are not merely elements of economic systems; they belong to larger social, cultural, and political wholes, and these are the arenas in which entrepreneurs must act. In Schumpeter's theory, entrepreneurship consists in linking together different on-going social practices in order to produce economic innovations. Entrepreneurs are agents of social change.

As a good economist, Schumpeter was interested in characterizing the 'entrepreneurial function' within the economic process. He located the sources of innovation, not in the machinelike operation of economic systems, but rather in persons. From the Schumpeterian perspective, capitalist economies are not 'self-propelling' – innovative economic growth in capitalism is initiated and sustained by individual actions. "The carrying out of new combinations," said Schumpeter, "we call 'enterprise'; the individuals whose function is to carry them out we call entrepreneurs."[10] Having laid out this analytical view of the entrepreneurial function, Schumpeter then went a step further and attempted to theorize the phenomenon of entrepreneurial formation. Schumpeter's understanding of entrepreneurship rests on a distinction between creative and rational action. Entrepreneurship exemplifies the former. Entrepreneurs are creative. A central feature of entrepreneurial action, then,

---

[9] See Joseph A. Schumpeter, Essays: On Entrepreneurs, Innovations, Business Cycles, and the Evolution of Capitalism, ed. Richard V. Clemence, New Brunswick, NJ: Transaction, 1989; especially, ch. 3, "The Instability of Capitalism"; ch. 18, "The Creative Response in Economic History"; and ch. 21, "Economic Theory and Entrepreneurial History." See, also, Joseph A. Schumpeter, The Theory of Economic Development: An Inquiry into Profits, Capital, Credit, Interest, and the Business Cycle, trans. Redvers Opie, New Brunswick, NJ: Transaction Books, 1983 [1926].

is 'non-rational,' and not amenable to conventional economic analysis. To account for this aspect of innovative change in economic life, Schumpeter interpreted entrepreneurship as a special kind of conduct undertaken by a special kind of person. He maintained that since entrepreneurship "essentially consists in doing things that are not generally done in the ordinary course of routine business, it is essentially a phenomenon that comes under the wider aspects of leadership."[11] This conception of entrepreneurship prompted Schumpeter to lend his theoretical and methodological allegiances to the study of economic history. He insisted that historical research remained indispensable in the study of entrepreneurial leadership (and in studies of a range of other economically relevant phenomena, including technological innovation, business cycles, capital formation, credit, and profits).[12] Like the members of the Austrian school, Schumpeter believed that economic modeling was too blunt a tool to capture in full the complexities and dynamics of the economic process. He concluded,

---

[10] Joseph A. Schumpeter, The Theory of Economic Development, New York: Harper, 1949 [1912]; p. 74.

[11] Joseph A. Schumpeter, "Economic Theory and Entrepreneurial History," p. 259. Sociologists have noted affinities between Schumpeter's ideas about entrepreneurial leadership and the Weberian concepts of rationalization and charisma. See, for example, Dahms, Harry F., "From Creative Action to the Social Rationalization of the Economy: Joseph Schumpeter's Social Theory," Sociological Theory 13, 1, 1995: 1-13; and Alberto Martinelli, "Entrepreneurship and Management," pp. 476-503 in The Handbook of Economic Sociology, ed. Neil J. Smelser and Richard Swedberg, Princeton, NJ: Russell Sage Foundation, 1994. Martinelli has this to say about the attenuated charisma that Schumpeter ascribed to successful entrepreneurs: "While having some elements in common with religious and military leaders of the past, the entrepreneur is, however, less heroic. He is a leader in a rational and antiheroic civilization, and as a result does not excite the charismatic feelings and collective enthusiasm of those who make or defend whole civilizations. Entrepreneurial leadership is not charged with the emotional elements that made the glory of other types of leaders...it operates in a more limited sphere and enjoys a more precarious status in society." Schumpeter's own pithy summary was this: "The stock exchange is a poor substitute for the Holy Grail." Joseph A. Schumpeter, Capitalism, Socialism, and Democracy, New York: Harper & Row, 1942 [1975]; p. 137.

[12] See Yuichi Shionoya, "Instrumentalism in Schumpeter's Economic Methodology," History of Political Economy 22, 1990: 187-22.

as well, that narrative histories of entrepreneurship could be profitably supplemented and enriched by psychological, anthropological, and sociological research and theorizing.[13]

Unfortunately, social research on entrepreneurship has proceeded down many disparate paths that remain unconnected. The field is conceptually fragmented. Investigations of entrepreneurial formation in the disciplines of psychology, anthropology, and sociology have typically asked two questions: 'What traits or characteristics distinguish entrepreneurs from others?' and 'What factors or conditions produce entrepreneurial persons and entrepreneurial actions?' Economists have traditionally sought to characterize the abstract features of the entrepreneurial function, and to understand the implications of entrepreneurial activities for larger economic processes, but analysts in sister social sciences have embraced different ends. They have concerned themselves with the origins and social histories of entrepreneurs and the social circumstances that give rise to entrepreneurial ventures. They have attempted to learn who entrepreneurs are and where they come from, and to explain why entrepreneurs do what they do. However, while accounting for the genesis of innovative enterprise is a goal shared by psychologists, anthropologists, and sociologists (along with sociologically minded economists), studies of

[13] Schumpeter's catholicism directly influenced members of the Research Center in Entrepreneurial History at Harvard University in the 1940s and 1950s. Schumpeter was loosely affiliated with the group. The Center became known for its sponsorship of interdisciplinary, theoretically eclectic, and historically inclined research. Members undertook studies of the 'entrepreneurial personality,' the social origins and social roles of entrepreneurs, and the institutional settings in which entrepreneurs emerge and operate. See Research Center in Entrepreneurial History, Harvard University, Change and the Entrepreneur: Postulates and Patterns for Entrepreneurial History, Cambridge, MA: Harvard University Press, 1949.

entrepreneurship in the social sciences have drawn wildly diverse conclusions. They have not converged on any unified theory.

In a recent review of the many literatures on the topic, Patricia H. Thornton proposes that social theories of entrepreneurship can be usefully classified as belonging to 'supply side' or 'demand side' schools.[14] The supply side approach focuses on the characteristics of entrepreneurs, and the social or cultural influences that produce entrepreneurial persons. Supply siders seek to locate the non-economic sources of entrepreneurial formation, and to explain distributions of entrepreneurial capacities among individuals within populations. Demand siders, by contrast, conceptualize entrepreneurship as a precipitate of various economic, technological, organizational, and institutional conditions. They attempt to account for the social production of entrepreneurial actions, not entrepreneurial persons. Demand side analyses examine relationships between innovative business projects and the contexts in which they occur.

THE SUPPLY SIDE

Most social scientists agree that entrepreneurs are made, not born, but there remain fundamental differences of opinion among them regarding how properly or best to explain appearances of entrepreneurial ventures. Supply-side psychologists attempt to distill the essential elements of the entrepreneurial personality, or quality of mind. Rather than analyzing constitutive features of entrepreneurial action – say, alertness or judgment – they look instead for personal endowments, temperaments, or

---

[14] Patricia H. Thornton, "The Sociology of Entrepreneurship," Annual Review of Sociology 25, 1999: 19-46; p. 21.

talents that are extrinsic and prior to the economic function itself. These may include independence, self-reliance, optimism, leadership, decisiveness, determination, perseverance, tolerances for ambiguity, uncertainty, and risk, among many others. Supply-side psychologists often start from the premise that entrepreneurs are distinguished by special psychological propensities, and they try to find out exactly what these propensities are. Many assume that explanations for fixed characteristics of this kind can be found in psychological histories. From their perspective, entrepreneurial persons are formed in developmental processes of socialization or mental adjustment.

Psychoanalytically inclined economic historian Bernard Sarachek, for instance, analyzed the family backgrounds of 187 American entrepreneurs in the 18th, 19th, and 20th centuries.[15] He examined, among other variables, the class status of families, fathers'occupations, entrepreneurs' relationships with their fathers, and birth orders of siblings. Sarachek concluded that economic deprivation and disrupted family relationships inculcated strong motivations for achievement in individuals making up a significant portion of his sample. His analysis constructs psychological foundations for 'rags-to-riches' tales. Another work by management scholars Erik K. Winslow and George T. Solomon presents a different interpretation. Winslow and Solomon suggest that entrepreneurs are "mildly sociopathic."[16] In this portrait of the enterprising psyche, business venturers act independently because they desire control

---

[15] Bernard Sarachek, "American Entrepreneurs and the Horatio Alger Myth," Journal of Economic History 38, 1978: 439-456.

[16] Erik K. Winslow and George T. Solomon, "Entrepreneurs Are More Than Non-Conformists: They Are Mildly Sociopathic," Journal of Creative Behavior 21, 1987: 202-213.

and distrust others' opinions. They break conventional rules and innovate because they are pathologically self-centered. Entrepreneurs, the authors contend, have little respect for social values. In their opinion, the entrepreneur is a deviant type. Others with proclivities for conformity and social approval are less likely to engage in entrepreneurial behavior.[17]

In a study of high-tech entrepreneurs, Edward B. Roberts offers yet another version of the 'entrepreneurial personality.' Roberts' work is an extended and highly eclectic study of commercial ventures spun out of the Massachusetts Institute of Technology.[18] He found a number of psychological similarities among the founders of these firms. Many were identified as 'inventor personalities' (clever, pragmatic, flexible, and solution-oriented) by their responses to the Myers-Briggs Type Indicator test. Many expressed moderate desires for independence and power and many appeared to have been influenced at a young age by self-employed fathers. Yet, none of the characteristics cited by Roberts comes close to being a prerequisite for, or a

---

[17] The contrast between this view and that of economist Mark Casson illustrates the vast differences that obtain among interpretations of entrepreneurial behavior. In Casson's view, entrepreneurs are not typically sociopathic – in fact, nothing could be further from the truth. Casson rejects entirely the notion that entrepreneurs are selfish economic opportunists. He proposes as the appropriate model of the entrepreneurial actor not 'economic man,' but rather 'ethical man.' According to Casson, entrepreneurs must be cooperative, reliable, and trustworthy. They must display personal integrity in marketplace cooperation and competition, and in political negotiations and conflicts. If they do not, their behaviors will be costly and will diminish their prospects for achieving their ends. See Mark Casson, Entrepreneurship and Business Culture: Studies in the Economics of Trust, Volume One, Edward Elgar: Aldershot, UK, 1995.

[18] Edward B. Roberts, Entrepreneurs in High Technology: Lessons From MIT and Beyond, New York: Oxford University Press, 1991; ch. 3. Roberts' analysis synthesizes (or, to put it another way, is a hodge-podge) of 'supply' and 'demand' side explanations. It incorporates a great deal of practical 'how to' advice, as well. In detailing his portrait of high-tech entrepreneurship at MIT, Roberts discusses – in addition to entrepreneurs' backgrounds and personal characteristics – technologies and R&D processes, organizational forms, financing, various business functions (e.g., management, product development, and marketing), and the institutional milieu of Cambridge and Greater Boston.

powerful predictor of, high-tech entrepreneurship. Roberts reports that correlations on a number of other demographic variables – especially age, education, and work experience – were more telling. On average, the founders of the MIT high-tech spin-off firms were well-educated engineers in their thirties with practical industrial design experience. Psychological make-ups aside, the MIT entrepreneurs were typically young and energetic enough to take on the tasks of company-building, and typically old and wise enough to know what they were doing, having acquired the experience and connections to prepare them for the rigors and demands of high-tech entrepreneurship.

Taken as whole, Roberts' study shows the inadequacy of accounts that rely exclusively on psychological traits or propensities to explain entrepreneurial behavior. They are too simplistic; they neglect the significance of 'external' structural and contextual factors. Supply-side psychologies of entrepreneurship have been roundly criticized for their narrow focus, and for the fact that they have not produced robust generalizations. Counterevidence abounds. It is reasonable to expect that the personalities or mental habits of entrepreneurs will matter and give rise, in a manner of speaking, to behaviors that shape outcomes in particular cases, but there does not appear to be any archetypal 'entrepreneurial psyche' shared by individuals who engage in innovative business practices. It is evident that entrepreneurial personalities and entrepreneurial motives and actions are too diverse to be captured in this manner. Because they conceptualize entrepreneurial 'drive' as a purely mental phenomenon, psychologists are ill-equipped to handle the empirical complexities of actual

entrepreneurial actions and practices. Supply-side sociologists have maintained that they do a better job of it.

Supply side sociologists argue that personality profiles fail as monocausal explanations of entrepreneurial activity because they ignore the ways in which individual psychologies and individual actions are shaped by social and cultural contexts. Instead of locating the sources of entrepreneurship exclusively in personal psychological histories and individual temperaments, they search for the antecedents of entrepreneurial attitudes and values in broader social and cultural environments. Some treat individual entrepreneurs as 'carriers' of culturally transmitted attitudes that encourage enterprise and innovation. The classic work in this genre is Max Weber's The Protestant Ethic and the Spirit of Capitalism. On the basis of extensive comparative-historical scholarship, Weber argued that the rational, systematic approach to business that characterizes modern capitalist enterprise issued originally from a number of non-economic social and cultural sources in the West, including, importantly, the doctrines of the Calvinism.[19] According to Weber, Calvinist beliefs prompted followers to adopt an attitude of 'worldly asceticism,' a mode of thought and action that the Calvinists translated into innovative business practices. Calvinism supplied the modern world with the original capitalist entrepreneurs.

Other influential supply-side analysts have constructed arguments along similar lines. In 1961, in a book called The Achieving Society, David McClelland

[19] Max Weber, The Protestant Ethic and the Spirit of Capitalism, trans. Talcott Parsons, New York: Charles Scribner's Sons, 1958 [1904-1905]. Among other contributing influences, Weber noted historical developments in law, political administration, and natural scientific inquiry.

likewise attempted to connect innovative economic growth with social values.[20] He observed that child-rearing practices in modern capitalist societies encourage independence, self-reliance, and personal excellence. In the process of socialization, he argued, children internalize these values and develop strong personal needs for high achievement. Later, many seek to satisfy these needs by becoming successful in business, and they are often willing to break with established conventions and patterns of action in order to do so. They become determined innovators. The structure of McClelland's explanation remained identical to Weber's, although within it, families rather than religious congregations are the important agents of socialization.

A year after McClelland published The Achieving Society, Everett Hagen introduced a theory that was similar in explanatory form, but very different substantively, and more ambitious in that it attempted to link micro and macro levels of analysis. Like McClelland's theory, Hagen's complex argument points to socialization and parent-child relationships as central to the formation of entrepreneurial personalities. However, Hagen also incorporated macrosocial variables as causal factors.[21] He observed that entrepreneurs are often overrepresented in social groups that suffer from status withdrawal or deprivation. According to Hagen, one positive response of families in such groups (among many negative reactions) is to foster creativity and a spirit of individualism in children. These

---

[20] David McClelland, The Achieving Society, Princeton, NJ: D. van Nostrand Co., 1961.

[21] Everrett E. Hagen, On the Theory of Social Change: How Economic Growth Begins, Homewood, IL: Dorsey, 1962.

disadvantaged individuals often develop mental habits that enable them to undertake innovative, entrepreneurial projects and to overcome social resistance.

Plenty of criticisms have been leveled at supply side analyses that attempt to explain entrepreneurial formation in terms of psychological conditioning or by reducing entrepreneurs to sociological 'types.' Management scholars Amit, Glosten, and Muller acknowledge that the complexities of entrepreneurs and their backgrounds have defied attempts to derive generally valid principles that can be use to predict appearances of innovators in particular times and places. In the study of entrepreneurial formation, they caution, "[i]t may be too ambitious to expect a complete and robust theory."[22] The histories and profiles of individual entrepreneurs are simply too diverse. Amit, et al. recite a long list of entrepreneurial qualities or characteristics that could have explanatory significance in particular instances:

> creativity, adaptiveness, technical know-how, vision and leadership ability, managerial and organizational skills, ability to make decisions quickly and to act in a rapidly changing and uncertain environment, personal integrity, a range of cognitive decision-making biases, and the entrepreneur's cultural background and education.[23]

Faced with this empirical complexity, Amit, et al. concede that the entire body of psychological and social psychological research on entrepreneurship has failed to deliver a coherent analytical picture of the genetic or experiential antecedents of entrepreneurial attitudes and values, or of personal qualities possessed by entrepreneurs that differentiate them from other people. "We simply do not know,"

---

[22] Raphael Amit, Lawrence Glosten, and Eitan Muller, "Challenges to Theory Development in Entrepreneurship Research," Journal of Management Studies 30, 1993: 815-834; p. 815.

[23] Amit, Glosten, and Muller, "Challenges to Theory Development in Entrepreneurship Research," p. 817.

they admit, "whether there is an essential set of entrepreneurial characteristics and what that set is."[24] Nevertheless, while psychoanalytic explanations appear to fail generally on empirical grounds, actors on the biotech stage still sometimes resort to them when it happens to suit their practical agendas. Alfred E. Middleton, for example, states that biotech entrepreneurs tend to be "smart, arrogant, single-minded, obsessive, highly egotistical, brutally honest, and loners by nature." They usually conform to this model, he asserts, because "[i]t takes a driven, singularly focused personality to overcome all of the hurdles in the path of any company startup."[25] Middleton, it should be noted, is a headhunter and vice-president of an executive search agency. He advertises a matchmaking service that delivers the best results when it locates the right person for a job. According to Middleton, the right person possesses, in addition to the necessary credentials, experiences, and skills, the proper temperament as well. The validity of Middleton's personality profile for entrepreneurs is questionable. No evidence is presented to support it, and counterexamples are plentiful. Of course, there is no reason to discount the significance of personal qualities in explanations of particular happenings in particular times and places, and persons who appear to fit Middleton's description may, in fact, make fine bioentrepreneurs. But it may be that (collective) entrepreneurial processes make entrepreneurial individuals rather than vice versa. In any event, no biotech

---

[24] Amit, Glosten, and Muller, "Challenges to Theory Development in Entrepreneurship Research," p. 817.

[25] See Alfred E. Middleton, "Pharmaceutical Execs Look to Biotech Careers," Biotechnology 7, 1989: 883-887.

entrepreneur has ever overcome hurdles to business or scientific success without assistance or purely by force of personality or individual will.

Many academic supply-siders have now largely dispensed with psychological accounting, electing instead to emphasize to a greater degree the social contexts in which entrepreneurs are formed. Some attribute supplies of willing and able entrepreneurs in a society – as does Hagen, ultimately – to the social circumstances of the particular groups from which they emerge. Unlike Hagen, however, researchers developing structural arguments do not assert that members of these groups tend to acquire distinctive psychological traits, nor are they concerned with specifying any particular set of attitudes or psychological propensities that characterize individual entrepreneurs. Rather, in this kind of accounting, the characteristics that matter are characteristics of groups or communities – their customs, practices, and patterns of association and communication. The idea that individuals adopt entrepreneurial ways of thinking and acting because they have been exposed to entrepreneurial ways of life and encouraged to embrace entrepreneurial values remains implicit, but in social structural accounts of entrepreneurial formation, the socialization of entrepreneurs is treated as an effect as well as a mediating cause.

Along this line of inquiry, Marxists and Schumpeterians have analyzed how, in capitalist societies, the bourgeois class produces entrepreneurs. Innovators emerge from the business elite because this group has at its disposable the means to protect its interests and further it ends. Bourgeois entrepreneurs are able to spur economic

growth because they are able to control private property and exercise political power.[26] However, not all entrepreneurs come from the ranks of the privileged. Many business scholars have focused their inquiries on the formation of entrepreneurship within ethnic minority groups.[27] Werner Sombart was the first scholar to theorize links between the social circumstances of minorities and processes of entrepreneurial formation. According to Sombart, the frequent appearance of entrepreneurs in minority populations is explained by the social marginality of these groups. As outsiders, so the argument goes, minorities often face discrimination. They are often denied access to social and economic resources and opportunities. In response, members of these groups develop particularized and innovative economic strategies and skills, as well as knowledge and material resources that they often share within the group. In analyses of this kind, the fact of relatively high levels of entrepreneurial activity within ethnic communities is traced to social structural conditions, and, in particular, to the disadvantaged positions of minorities. The successes of minority entrepreneurs are attributed to in-group solidarity, to the functioning of networks of

---

[26] See, for example, Maurice H. Dobb, "The Entrepreneur Myth," pp. 3-15 in On Economic Theory and Socialism: Collected Papers, London: Routledge & Kegan Paul, 1955; Karl Marx, Capital, Vol. 1, trans. Ben Fowkes, New York: Vintage Books, 1977; William Miller, "The Business Elite in Business Bureaucracies," pp. 286-305 in Men in Business: Essays in the History of Entrepreneurship, ed. Cambridge, MA: Harvard University Press, 1952; Joseph A. Schumpeter, Capitalism, Socialism, and Democracy, New York: Harper, 1942. Strictly speaking, Marxism does not qualify as a supply-side theory. Marxists do not analyze the processes in which individual entrepreneurs are formed. For them, the role of the entire bourgeois class is to revolutionize perpetually the means of capitalist production.

[27] See, for example, Howard E. Aldrich and Roger Waldinger, "Ethnicity and Entrepreneurship," Annual Review of Sociology 16, 1990: 111-135; Gillian Godsell, "Barriers to Entrepreneurship in South Africa," pp. 85-98 in The Culture of Entrepreneurship, ed. Brigitte Berger, San Francisco, CA: ICS Press; Alejandro Portes, and Min Zhou, "Gaining the Upper Hand: Economic Mobility Among Immigrant and Domestic Minorities," Ethnic and Racial Studies 15, 1992: 491-522; Roger Waldinger, Robin Ward, and Howard E. Aldrich, "Ethnic Business and Occupational Mobility in Advanced Societies," Sociology 19, 1985: 586-597; Robin Ward and Richard Jenkins, eds. Ethnic Communities in Business: Strategies for Economic Survival. Cambridge: Cambridge University Press, 1984.

communication, exchange, and cooperation within ethnic communities.[28] For Sombart, and many other scholars since, the social rather than the individual characteristics of entrepreneurs are the keys to understanding entrepreneurial formation.

Numerous quantitative studies have confirmed social structural patterns in the phenomenon of high-tech entrepreneurship. To the surprise of no one familiar with the dynamics of social life in high-tech industries, active participation in technical communities and organizations prepares founders of high-tech companies for their social roles.[29] These persons are minority entrepreneurs, too. They have educational and technical backgrounds that distinguish them from most others. They tend to travel in circles where contributions to progress in science, engineering, and business are valued and rewarded. Their social connections afford them access to funds of knowledge and skill that are useful to efforts to commercialize new inventions or to develop products from the findings of scientific investigations. Their experiences in the sciences, engineering, and business teach them how to identify and secure the materials and financial assistance that they will need to make successes of their own private ventures. In the specific case of the biotech sector of the pharmaceutical industry, the original entrepreneurs in the field were drawn almost exclusively from communities of academic life scientists and medical researchers, along with

---

[28] Werner Sombart, The Quintessence of Capitalism: A Study of the History and Psychology of the Modern Business Man, trans. M. Epstein, New York: H. Fertig, 1967 [1915]; The Jews and Modern Capitalism. Trans. M. Epstein, Glencoe, IL: Free Press, 1951 [1913].

[29] Edward B. Roberts, Entrepreneurs in High Technology: Lessons From MIT and Beyond, New York: Oxford University Press, 1991.

occasional deserters from the ranks of venture capitalists. Later, scientists and executives from the pharmaceutical industry (including the biotechnology sector) began to make more frequent appearances.[30] The life sciences and the pharmaceutical business in the late 1970s and early 1980s were the antediluvian pools from which new entrepreneurs crawled to initiate the evolution of biotechnology industry. This is a sociological fact that no one disputes.

Of course, unlike new immigrants who rely on each other to scratch out livelihoods in unfamiliar surroundings, the minorities to which biotech entrepreneurs tend to belong are social elites. Overrepresented among the officers of new biotech companies have been alumni and faculty of the finest and most well-endowed research universities, members of prestigious professional societies and associations in the sciences and medicine, and employees of large corporations and federal government agencies. The social distances that separate most prospective bioentrepreneurs from money, power, and information are not great. The manners that they affect, the languages that they speak, the cloths that they don, and the degrees of social status and prestige that they enjoy by virtue of their professional and social affiliations smooth passages through financial and scientific networks to capital, human resources, and

---

[30] Mark D. Dibner, "Commerical Biotech's Founding Fathers," Biotechnology 5, 1987: 571-572. In the 1970s, only 27.6% of new biotech companies were founded or co-founded by persons with experience in the pharmaceutical industry. By the mid-1980s, industry people were involved in 66.2% of all new foundings. During this period, there was also a decline in the average size of the pharmaceutical and biomedical companies with which founders were previously affiliated. From the beginning, the majority of entrepreneurs starting companies to develop biological diagnostics or to manufacture new life science instruments, supplies, and reagents came to their projects from industrial settings. And through the mid-1980s, only 5.4% of company founders were women. These facts and trends are not mysterious for persons familiar with the life sciences and the biotech industry in its infancy, but the explanations that make sense of these 'structural' facts are contextual – i.e., historical, cultural, and idiographic.

other material ingredients vital to successful scientific entrepreneurship. Social scientists studying social networks and inter-organizational communications and collaborations have lately produced numerous maps that chart the social locations and movements of individuals, including entrepreneurs,[31] and firms and institutions participating in these processes.[32] Because of their inclusion in minority groups with connections to social elites, and because of the dynamics and structural characteristics of high-tech industries (for which they are partly responsible), bioentrepreneurs rarely have to travel far across social or geographics spaces in order to visit money, power, or knowledge.[33]

---

[31] David Blumenthal, "Academic-Industry Relationships in the Life Sciences: Extent, Consequences, and Management," Journal of the American Medical Association 268, 23, 1992: 3344-3349; Blumenthal, David, et al., "Participation of Life Science Faculty in Research Relationships with Industry," New England Journal of Medicine 335, 23, 1996: 1734-1739; Mark D. Dibner, "Commerical Biotech's Founding Fathers," Biotechnology 5, 1987: 571-572; Karen Seashore Louis, et al., "Entrepreneurs in Academe: An Exploration of Behaviors Among Life Scientists," Administrative Science Quarterly 34, 1989: 110-131; Lynne G. Zucker and Michael R. Darby, "Virtuous Circles of Productivity: Star Bioscientists and the Institutional Transformation of Industry," Working Paper #5342, National Bureau of Economic Research, Cambridge, MA, 1995.

[32] Joel A.C. Baum, Tony Calabrese, and Brian S. Silverman, "Don't Go It Alone: Alliance Composition and Startups' Peformance in Canadian Biotechnology," Strategic Management Journal 21, 3, 2000: 267-294; Koenraad Debackere and Bart Clarysse, "Advanced Bibliometric Methods to Model the Relationship Between Entry Behavior and Networking in Emerging Technological Communities," Journal of the American Society for Information Science and Technology 49, 1, 1998: 49-58; Loet Leydesdorff and Gaston Heimeriks, "The Self-Organization of the European Information Society: The Case of Biotechnology," Journal of the American Society for Information Science and Technology 52, 14, 2001: 1262-1274; Amalya L. Oliver and Julia Porter Liebeskind, "Three Levels of Networking for Sourcing Intellectual Capital in Biotechnology," International Studies of Management and Organization 27, 4, 1997-98: 76-103; Luigi Orsenigo, Fabio Pammoli, and Massimo Riccaboni, "Technological Change and Network Dynamics: Lessons from the Pharmaceutical Industry," Research Policy 30, 3, 2001: 485-508; Jason Owen-Smith, Massimo Riccaboni, Fabio Pammoli, and Walter W. Powell, "A Comparison of U.S. and European University-Industry Relations in the Life Sciences," Management Science 48, 1, 2002: 24-73; Walter W. Powell, Kenneth W. Koput, and Laurel Smith-Doerr, "Interorganizational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology." Administrative Science Quarterly 41, 1996: 116-145; Walter W. Powell and Jason Owen-Smith, "Universities and the Market for Intellectual Property in the Life Sciences," Journal of Policy Analysis and Management 17, 2, 1998: 253-277.

[33] See, for example, Walter W. Powell, et al., "The Spatial Clustering of Science and Capital: Accounting for Biotech Firm-Venture Capital Relationships," Regional Studies 36, 3, 2002: 291-305.

THE DEMAND SIDE

A criticism leveled at all supply side variable analyses – whether they cite individual psychologies, elements of culture, or social structural conditions as causal factors – is that they rely on static explanatory models. Because they typically dismiss contextualizing histories as anecdotal evidence, supply side number crunchers are unable to conceptualize the ways in which social processes transform cultures and social-structural patterns, and impact the conditions of entrepreneurship. They fail to take into account the changes wrought in capitalist societies by innovative business practices. These are problems that demand side explanations attempt to remedy. Demand side theories of entrepreneurship do not ask the question 'Where do entrepreneurs come from?' Instead, they ask 'Where do opportunities for entrepreneurship come from?' and 'What do entrepreneurs do, and why?' When it comes to accounting for innovative business practices, supply siders want to know 'What kind of person would think to do such things?' Those working the demand side, by contrast, want to know 'What made it possible for anyone so inclined to do such things?' They also ask, 'How are such things done?' and 'What are the results?'

Accordingly, demand side theorists are not much concerned with the psychological or demographic attributes of entrepreneurs. They do not contest the idea that certain individuals, for a wide range of reasons, may be predisposed to engage in innovative enterprise. Neither do they reject the notion that cultural values or social practices of certain social groups may foster entrepreneurial attitudes. They deny, however, that specific psychological attributes, cultural influences, or social characteristics can be invoked as necessary or sufficient causes of actual

entrepreneurial behaviors.[34] The 'fire in the belly' of the entrepreneur is considered incidental and disallowed as an explanation, as is general social approval of innovative commercial practices. For demand theorists, analyses that rely on personal qualities, collective entrepreneurial strategies, or generalized cultural attitudes to account for appearances of new ventures commit the error of 'sampling on the dependent variable.'[35]

They argue that attitudes, intentions, and plans do not necessarily distinguish successful and unsuccessful entrepreneurial ventures. Under favorable conditions, they point out, lackadaisical, inept, and poorly-connected persons may blunder into success; under unfavorable conditions, determined, talented, and well-connected people may fail, or never even have a chance to get started.

In demand side analyses, processes of entrepreneurial formation are dismissed as both analytical problems and explanatory resources. The formation of individual entrepreneurs requires no accounting. It is assumed that when structural or environmental conditions are right for the founding of new ventures, new entrepreneurs will rise to the occasion. The supply of entrepreneurial persons in populations is simply taken for granted. From the demand perspective, actual entrepreneurial actions are not explained by conditions that affect the supply of entrepreneurs willing to engage in them, but rather by conditions that allow actors to undertake them. When environmental conditions permit or encourage entrepreneurial

---

[34] William B. Gartner, "Who is an Entrepreneur?" Is the Wrong Question," Entrepreneurship: Theory & Practice 13, 1988: 47-68.

[35] Sidney M. Greenfield and Arnold Strickon, "A New Paradigm for the Study of Entrepreneurship and Social Change," American Journal of Sociology 87, 1981: 467-499.

innovation, people evidently move to take advantage of such openings. This kind of context-bound behavior is where demand side studies begin. The empirical focus of demand side research is on contextual action – what individuals and groups actually do in relation to their social and economic surroundings. Demand side analysts seek to explain, not the social production of entrepreneurial persons, but rather the social production of entrepreneurial projects.

So, this perspective examines the environmental contexts of entrepreneurial behavior. Demand siders seek to identify economic, organizational, and social structural factors that influence and encourage (or discourage) entrepreneurial activity. They attempt to link rates of entrepreneurial activity with, for example, the logic of class conflict in capitalist society,[36] organizational forms and processes,[37] structures of social networks,[38] concentrations of investment capital,[39] conditions in stock and business acquisition markets,[40] etc. The aim is specify the conditions that provide persons or groups with entrepreneurial opportunities and resources required to take

---

[36] Maurice H. Dobb, "The Entrepreneur Myth," pp. 3-15 in On Economic Theory and Socialism: Collected Papers, London: Routledge & Kegan Paul, 1955; Karl Marx, Capital, Vol. 1, trans. Ben Fowkes, New York: Vintage Books, 1977.

[37] Jeffrey G. Covin and Dennis P. Slevin, "A Conceptual Model of Entrepreneurship as Firm Behavior," Entrepreneurship: Theory & Practice 16, 1991: 7-25; John Freeman, "Entrepreneurs as Organizational Products: Semiconductor Firms and Venture Capital Firms," Advances in the Study of Entrepreneurship, Innovation, and Economic Growth 1, 1986: 33-52.

[38] Ronald S. Burt, Structural Holes: The Social Structure of Competition, Cambridge, MA: Harvard University Press, 1992.

[39] Richard L. Florida and Martin Kenney, "Venture Capital-Financed Innovation and Technological Change in the U.S.A," Research Policy 17, 1998: 119-137; Richard L. Florida and Martin Kenney, "Venture Capital, High Technology, and Regional Development," Regional Studies 22, 1998: 33-48.

[40] Michael A. Hitt, Robert E. Hoskinson, Richard A. Johnson, and Douglas D. Moesel, "The Market for Corporate Control and Financial Innovation," American Management Journal 39, 1996: 1084-1119.

advantage of them. They assume that their investigations of concrete situated actions will show that the conditions of entrepreneurship are variable and subject to change, and will allow them to track the ways in which successful entrepreneurial innovations feed back into and reshape social environments.

The classical demand side analysis of entrepreneurship was provided by Karl Marx. For Marx, innovative enterprise is explained by the inexorable historical workings of the social and economic logic of capitalism. According to Marx, modern forms of private property, technological innovation, and entrepreneurship all emerged simultaneously with the historical formation of the bourgeois and proletarian social classes and the capitalist mode of production in Western Europe. His was a fully systemic explanation. The capitalist system demands that individuals participate – as a matter of economic survival – in the continual refinement of production techniques, the creation of profits, the generation of economic growth, and the concentration of capital. The class situation of individuals determines the particular roles that they play in these processes. Members of the bourgeois class are compelled by material interests to act as entrepreneurs (just as proletarians are compelled to sell their labor power). Capitalist entrepreneurship consists in the organization, control, and exploitation of materials and labor in ways that contribute to the accumulation of capital. In Marxist economics, no other explanation for innovative enterprise is necessary.

Most demand side analysts consider the Marxist approach to be too simplistic. Clearly, certain conditions and circumstances within capitalist economies favor technological and organizational innovations and the emergence of new firms, while

others inhibit this kind of growth. In order to investigate entrepreneurial responses to dynamic and emergent social and economic conditions in particular cases and circumstances, many demand siders have adopted a 'situational' approach. For example, in a widely influential paper, William P. Glade proposed that the best way to understand innovative enterprise is to examine the specific economic, organizational, institutional, and political conditions that, for situated individuals and groups, comprise a field of action. Fields of this kind dictate a range of possible forms that entrepreneurial behavior can take.[41] Actual entrepreneurial actions, says Glade, are configured, at any given point in time, by objective opportunity structures. The choices available to actors within these structures are transformed as environments change. Empirical instances of entrepreneurship will vary in form, depending on the circumstances, but they can always be understood, in part, as results of context-bound choices. The job of the researcher, then, is to audit in detail the concrete choices made by entrepreneurs, and to discern precisely how these choices were shaped or constrained by entrepreneurs' circumstances.

Lately, broadly similar evolutionary and ecological approaches have become popular among demand side analysts.[42] Like Glade, these analysts hold that entrepreneurship cannot be precisely defined, but can be understood by clarifying how entrepreneurial behaviors fit into and are shaped by dynamic environments. They

---

[41] William P. Glade, "Approaches to a Theory of Entrepreneurial Formation," Explorations in Entrepreneurial History 4, 1967: 245-259.

[42] Sidney M. Greenfield and Arnold Strickon, "A New Paradigm for the Study of Entrepreneurship and Social Change," American Journal of Sociology 87, 1981: 467-499; Sidney M. Greenfield and Arnold Strickon, Entrepreneurship and Social Change, Lanham, MD: University Press of America, 1986;

dismiss, however, Glade's notion that the fields of action on which entrepreneurs operate can be fixed for analysis and called 'structured' or 'objective.' They adopt a more processual view. Evolutionary and ecological approaches assume that entrepreneurship is a phenomenon that emerges as the result of ongoing interactions between entrepreneurial projects, on the one hand, and the environments in which these projects are undertaken, on the other. In this kind of analysis, neither structure nor action is determinative. The weight of explanation is delegated instead to interactions between behaviors (individual and collective) and environments that either smile or frown on them. The process of economic innovation is conceptualized as one in which dynamic contexts shape situated actions, and, simultaneously, one in which situated actions shape dynamic contexts.

In evolutionary and ecological approaches, there has been a shift away from detailed investigations of specific entrepreneurial behaviors toward the computation of 'rates' of entrepreneurial or innovative activity.[43] Populations of firms are often selected as units of analysis. The aim is derive general statements about the kinds of interactions that constitute or prevent innovative growth in organizational ecosystems. For example, it may be that in certain environmental processes, small firms tend to be 'fittest,' to prove more 'adaptive,' or to exhibit greater 'functionality.' In other environments, innovations sponsored by large corporations may tend to flourish while

---

Michael T. Hannan and John Freeman, Organizational Ecology, Cambridge, MA: Harvard University Press, 1989.

[43] Howard E. Aldrich, "Using an Ecological Approach to Study Organizational Founding Rates," Entrepreneurship: Theory & Practice 14, 1990: 7-24; Howard E. Aldrich and Gabriele Wiedenmayer, "From Traits to Rates: An Ecological Perspective on Organizational Foundings," Advances in Entrepreneurship, Firm Emergence, Growth 1, 1993: 145-195.

those introduced by smaller competitors flounder. Evolutionary and ecological analysts maintain that, in order to find out what kind of environment one is dealing with, and what kinds of interactions and entrepreneurial projects are favored within it, it is necessary to identify abstract statistical patterns of successes and failures. These are taken to indicate general evolutionary principles that account for the environmental selection of certain kinds of innovations and the environmental withering of others within definite temporal, geographic, and social boundaries.

THE EMBEDDEDNESS OF ENTREPRENEURSHIP

Evolutionary and ecological approaches have been criticized on the grounds that they lack a theory of agency. Confining their empirical focus to the features of organizational populations and the processes that characterize them, they tend to neglect the substance of entrepreneurial actions undertaken by persons, and so, often fail to credit as causal factors the unique contributions that entrepreneurial people make to processes of innovation. What ultimately distinguishes an entrepreneurial success from an entrepreneurial failure in the ecological 'paradigm' is environmental selection, and not the ingenuity, judgment, or skill of the entrepreneur. The main theoretical point of evolutionary and ecological approaches, as far as individuals are concerned, is that timing and luck are as important to success in specific instances, and sometimes more important, than individual skill, judgment, or perseverance, for these do not guarantee success. For firms, the lesson is that the ecological fit of an organizational form determines outcomes rather than the form itself, for the efficacy or functionality of such characteristics are variable and context-dependent.

Demand side approaches have remedied some of the problems associated with supply side accounts, but they have not managed to produce a wholly satisfactory portrait of entrepreneurship, one that captures all of the empirical complexities of the phenomenon. In Patricia Thornton's view, both supply and demand-side explanations of entrepreneurship tend too often toward reductionism. For this reason, she suggests that the way forward for social studies of entrepreneurship in the present is to develop integrative approaches that make use of insights derived from both supply and demand side inquiries, while avoiding the sins of omission that each commits. Thornton's recommendation is to consider the 'embeddedness' of entrepreneurial actions and practices in webs of social relations without granting special explanatory privilege to either psychological or cultural antecedents of entrepreneurship, situated entrepreneurial plans and actions, or contextual factors that enable and constrain entrepreneurial efforts.[44] In other words, she urges analysts to treat entrepreneurship as both a 'dependent' and 'independent' variable. She points out that it is possible to examine simultaneously how entrepreneurship arises, as Brigitte Berger writes, from "a tangled web of demographic, legal, technological, material, ideational, and cultural influences,"[45] how circumstances define the forms and consequences of entrepreneurial decisions and actions, and also how particular entrepreneurial actions impact, sometimes dramatically, the environments in which they appear.

---

[44] Patricia H. Thornton, "The Sociology of Entrepreneurship," Annual Review of Sociology 25, 1999: 19-46; p. 23-41; Mark S. Granovetter, "Economic Action, Social Structure, and Embeddedness," American Journal of Sociology 91, 1985: 481-510.

[45] Brigitte Berger, "Introduction," pp. 1-12 in The Culture of Entrepreneurship, ed. Brigitte Berger, San Francisco, CA: ICS Press, 1991; p. 2.

As an example of a study of 'embedded' entrepreneurship, Thornton cites a report on U.S. semiconductor start-ups conducted by Eisenhardt and Schoonhoven.[46] In this work, the authors analyzed various dimensions of high-tech entrepreneurship, including elements of entrepreneurial formation (how entrepreneurs' backgrounds, prior work experiences, and social ties contributed to a supply of willing and able venturers in the semiconductor industry); elements of entrepreneurial action (the practical strategies that individuals and groups employed in order to establish new companies); as well as the impacts of broader environments in which the start-ups emerged (i.e., the ways in which institutional and economic contexts affected the organizational forms, tasks, and prospects of the new ventures). The agenda in studies of this kind is not to explain entrepreneurial formation, entrepreneurial behaviors, contexts of entrepreneurial action, or their interrelations. If the notion of 'embeddedness' is taken seriously, then the way to proceed with investigations of entrepreneurship is instead to chronicle and understand how entrepreneurial processes unfold. In the course of investigating the emergence of entrepreneurial ventures from this perspective, analysts can address demand side concerns by asking 'How, under specific conditions, have people gone about achieving entrepreneurial success (or how did they fail to do so)?' They can also ask and answer supply side questions about entrepreneurial formation, e.g., 'How did particular individuals and groups become capable of doing such things?' These are the questions asked in this study of San Diego biotechnology.

---

[46] Kathleen M. Eisenhardt and Claudia Bird Schoonhoven, "Organizational Growth: Linking Founding Teams, Strategy, Environment, and Growth Among U.S. Semiconductor Ventures," Administrative Science Quarterly 28, 1990: 274-291.

HERMENEUTICS AND ENTREPRENEURSHIP

The aim of this dissertation is to examine the concrete substance of entrepreneurial formation and entrepreneurial action. If an articulated theoretical basis is wanted for studying entrepreneurship in this way, economist Don Lavoie has provided one.[47] Lavoie endorses, in a qualified manner, the subjectivism of the Austrian School economists. The subjectivist approach is a reaction against classical economic theory. The Austrians rejected the basic classical assumption that economic action consists in choices made within objective opportunity structures by perfectly informed individuals. The Austrian alternative assumes the following: in real life economics, actors are not perfectly informed; some know more than others, and none knows all. Obviously, there are incentives to search for information; those who discover first what was previously unknown about a market enjoy an economic edge. Those who move to exploit such advantages are called entrepreneurs. The Austrians, unlike classical theorists, considered entrepreneurial action a central motive force in the economic process. Lavoie concurs with the Austrians on this much, pointing out that human ingenuity, innovative entrepreneurship, and economic change are either misrepresented or simply inexplicable within the classical framework: "Entrepreneurship," he says, "should include genuine novelty and creativity and should not be rendered as a mechanical search for pre-existing profit opportunity."[48]

---

[47] Don Lavoie, "The Discovery and Interpretation of Profit Opportunities," pp. 33-51 in The Culture of Entrepreneurship, ed. Brigitte Berger, San Francisco, CA: ICS Press, 1991.

[48] Don Lavoie, "The Discovery and Interpretation of Profit Opportunities," p. 36.

Lavoie eventually parts company with the Austrians, however, and, in particular, with Israel Kirzner's theory of entrepreneurship, on methodological and epistemological points. Kirzner described alertness to profit opportunities as the defining feature of entrepreneurial action. A thorough empirical account of entrepreneurship, on Kirzner's view, must represent this quality by referring to the situated knowledge, plans, and perceptions of the individual subject. For Lavoie, this bit is unobjectionable. However, in Kirzner's theoretical scheme, when alertness has been illuminated in this way – i.e., in terms of individual cognition – then, for the economist's purposes, the account is sufficient and complete. Lavoie disagrees. He rejects this kind of methodological individualism and notes that the Austrian approach is premised on an empiricist epistemology. The Austrians assumed that objective economic opportunities await discovery by alert individuals, much like seashells, bottles, or pieces of driftwood thrown up on beaches. Entrepreneurs simply find them first – because they are alert – and act to profit from them. Against this interpretation, Lavoie argues: "Most acts of entrepreneurship are not like an isolated individual finding things on beaches; they require efforts of the creative imagination, skillful judgments of future cost and revenue possibilities, and an ability to read the significance of complex social situations."[49]

To theorize creative, skillful, and meaning-laden efforts of this kind, Lavoie adopts a hermeneutic approach. He argues that market opportunities reside in the midst of concrete historical and cultural processes, that they are defined by their situations in these processes, and that because this is so, discovering an opportunity

[49] Don Lavoie, "The Discovery and Interpretation of Profit Opportunities," p. 44.

entails much more than simply perceiving it. According to Lavoie, market discovery consists in understanding what an opportunity means in relation to numerous surrounding spheres of action and constellations of meaning. (For biotech entrepreneurs, the relevant spheres of action and constellations of meaning are scientific disciplines, universities, the pharmaceutical industry, medicine and the health care delivery system, the venture capital business, the stock market, and government regulatory agencies, among others).[50] Only by being informed generally about what is possible and probable within established patterns of meaningful conduct relevant to an opportunity or an imagined enterprise can an alert entrepreneur begin to understand what has been found and what can be done with it. Without interpreting found opportunities in this way, it would be impossible to see the potential for profit in them. For Lavoie, entrepreneurial discovery is an interpretive process:

> ...this reading of profit opportunities necessarily takes place within a larger context of meaning, against a background of discursive practices, a culture. That is to say, entrepreneurship is not so much the achievement of the isolated maverick who finds objective profits others overlooked as it is of the culturally embedded participant who picks up the gist of a conversation.[51]

In effect, for the subjectivism of the Austrian School of economics, Lavoie substitutes the 'intersubjectivism' of interpretive sociological approaches. This prescription provides a theoretical entrée to the concrete social, cognitive, and moral elements of entrepreneurship that sociological variable analyses have trouble representing. From an interpretive sociological point of view, it is evident that a large

---

[50] I discuss these broad historical, cultural, and social-structural contexts of bioscientific entrepreneurship at length below, in chapters three and four.

[51] Don Lavoie, "The Discovery and Interpretation of Profit Opportunities," p. 36.

part of entrepreneurship consists in learning about social things, in working with people, making judgments about people, and soliciting faith and goodwill from people. Entrepreneurs everywhere are obliged, if they are to be successful, to persuade others to join in their projects, to base their business decisions on practical knowledge of human beings and social processes, and to establish and sustain relationships of trust and exchange. Lavoie's interpretive theory of entrepreneurship is a sociological theory. It calls implicitly for empirical sociological investigations of entrepreneurial formation, entrepreneurial behavior, and entrepreneurial contexts together as constitutive elements of the entrepreneurial process. Its conceptualization of entrepreneurship as a process in which social learning figures prominently is a tacit endorsement of historical and ethnographic research on entrepreneurial careers and the collective actions-in-context that comprise entrepreneurial projects.

The notion that only historical inquiries can yield substantive understandings of entrepreneurship was first and influentially advanced long ago by Schumpeter. Consequently, all historical studies of entrepreneurial innovation that focus on actions and persons can be called 'Schumpeterian,' in some sense. Yet, Schumpeter contrasted creative action and entrepreneurial values with pure rational calculation, and with the conservative attitudes of the manager. This view encourages certain misunderstandings about entrepreneurship. Following this familiar line of thinking, academic analysts have rarely questioned the notion that the tasks, mind-sets, and ways and means of entrepreneurs (whether conceptualized as causes, effects, or as 'socially embedded' phenomena) are fundamentally different than those of managers and accountants (who are often caricatured as inveterate order-keepers).

Entrepreneurs innovate and create, it is said; they break molds and disregard rules. Managers and accountants, on the other hand, conserve and control; they operate within the confines of established hierarchies. They aim to preserve order by following and enforcing rules. Lavoie's approach suggests a way to reconceptualize this contrast, to break down the dichotomy between entrepreneurship, on the one hand, and management and accounting (along with other forms of routine profiteering), on the other, and to demystify entrepreneurial action.

Entrepreneurs, says Lavoie, join in social conversations in order to make things happen. The same can be said of managers. The successful manager listens to the desires, complaints, and demands of existing and potential employees and tries to shape an attractive work environment that will persuade new workers to sign on and old ones to stay, and to contribute their energies and skills to production. The successful manager listens to the plural discourses that constitute dynamic organizational processes and tries to establish and maintain workable interfaces between intraorganizational groups. Managers do this in order to protect subordinates, cooperate with horizontal peers, and satisfy superiors. They typically attempt to harmonize the interests and ends of people situated variously in their organizations, and elsewhere, too. Entrepreneurs and managers have different concrete goals and they are obliged to converse with different groups in order to accomplish them, but, in the abstract, as Lavoie has conceptualized it, entrepreneurship and management both consist in talking, listening, and acting in ways that are sensitive to the character and substance of ongoing social processes. They both require the same sort of creative participation in social interactions. What makes both entrepreneurs and managers

successful (along with a bit of luck) is their ability to join social conversations and nudge them in desired directions.

Many students of entrepreneurship have too readily accepted the idea that, in relation to other forms of activity (and management is often offered as a prime example), there is something special and extraordinary about entrepreneurial behavior. They often assume that some intrinsic quality distinguishes entrepreneurial action from ordinary action. Certainly, when entrepreneurs succeed, observers may interpret their successes as special, admirable results. They may value highly what entrepreneurs accomplish, and they may applaud economic and social changes engendered by entrepreneurial efforts. It is a mistake, however, to assume that innovative projects can be accomplished only by extraordinary means and extraordinary people.[52] Some supply side theories of entrepreneurship do just this. In order to explain the emergence of innovative enterprises, they attempt to formulate some distinctive 'essence' of entrepreneurship. To account for innovative behaviors, they often resort to talk about ineffable qualities of the entrepreneur – e.g., 'vision,' 'spirit,' or 'drive.' It is not necessarily wrong to impute special personal qualities to individuals basking in the glow of success. They may well possess some. However, while entrepreneurship may be, by definition, innovative, it is still possible to appreciate the results of successful entrepreneurial efforts without concluding that they must have been produced by a special kind of action or a special kind of person.

---

[52] The idea that entrepreneurial discovery, while innovative, is still an 'ordinary' activity resonates with recent claims made by sociologists of science to the effect that scientific discovery, another form of innovative action, is likewise 'ordinary.' See Michael Lynch, Scientific Practice and Ordinary Action: Ethnomethodology and Social Studies of Science. Cambridge: Cambridge University Press, 1993.

It is easy, with talk about such things as vision, spirit, and drive, to fashion misleading representations of entrepreneurship and entrepreneurial persons. Aldrich and Fiol, for instance, note that imputations of special powers to entrepreneurs in cases of success are dependent on prior imputations of ordinary qualities (or worse) when outcomes were uncertain. Before they have demonstrated their capacities to create despite forces of inertia or purposeful resistance working against them, entrepreneurs can seem foolhardy:

> From an institutional and ecological perspective, founders of new ventures appear to be fools, for they are navigating, at best, in an institutional vacuum of indifferent munificence and, at worst, in a hostile environment impervious to individual action. In addition to the normal pressures facing any new organizations, they must also carve out a new market, raise capital from skeptical sources, recruit untrained employees, and cope with other difficulties stemming from their nascent status.[53]

Some entrepreneurs may be fools, but not all are. This general characterization appears reasonable only when the practical work that entrepreneurs do and the practical knowledge that they employ to do it are overlooked. Certainly, if one estimates the magnitude of entrepreneurial tasks without also assessing the resources that entrepreneurs can muster and the strategies that they can devise to accomplish them, then obstacles in paths to profit may appear insurmountable. In the event that entrepreneurs do, in fact, overcome such obstacles, if distant observers are not aware of how they managed to do it and who helped them, then their successes can appear miraculous. But individual entrepreneurs do not start from nowhere. Usually, when

---

[53] Howard E. Aldrich and C. Marlene Fiol, "Fools Rush In? The Institutional Context of Industry Creation," Academy of Management Review 19, 1994: 645-670. Aldrich and Fiol do not believe that entrepreneurs are fools. They emphasize that entrepreneurs must secure social legitimacy for their

they undertake a venture, they already possess funds of knowledge, material resources, and social connections that they can summon to confront some of the challenges that they have posed for themselves. Sometimes these funds may be insufficient. Surely, many entrepreneurs overestimate their chances, or plainly have not amassed necessary knowledge or information, or secured access to resources that they will need. These persons can rightly be called foolhardy. Still, when ventures succeed, unless one has examined closely just how entrepreneurs achieved their ends, it is gratuitous to say that only extraordinary persons could have defeated the traps and obstacles in their paths. When analysts neglect the practical social engineering that entrepreneurs must undertake – i.e., mobilizing the necessary social, economic, and political support, usually from a wide variety of sources – they tend to portray entrepreneurs as reckless gamblers or charismatic movers and shakers. Some individual entrepreneurs may be reckless, and some may be charismatic, but this kind of talk glosses over the substance of entrepreneurship and over the practical sense embedded in the situated plans and actions that entrepreneurs formulate and carry out in order to tackle the difficult and uncertain tasks of innovative enterprise.

I think it is reasonable to start, as does Lavoie, from the assumption that most entrepreneurs – or, at least, most of those who actually get started – are not foolish, but rather knowledgeable. If this is right, then understanding entrepreneurial projects requires learning what entrepreneurs are knowledgeable about, and how they become knowledgeable. From this perspective, empirical research on entrepreneurship ought

---

projects in order to succeed – so, from their perspective, entrepreneurs become geniuses only when they win, and fools only when they lose.

to focus on just how entrepreneurs become informed about the practical tasks that they take on, and just how in practice they employ lessons derived from experience in order to accomplish their tasks. Lavoie does not talk about special qualities of innovators. He gives no reason to doubt that individual entrepreneurs are often perceptive, enthusiastic, and determined, but his theory suggests, in effect, that when entrepreneurs succeed, it is usually because they know what they're doing. In his view, the substance of entrepreneurship is informed participation in social processes. Entrepreneurs, according to Lavoie, prosper by learning about and coming to understand the logics of numerous social processes unfolding around them. They utilize social knowledge derived from practical experience to formulate effective strategies and plans and carry them through.

So, when entrepreneurs achieve their goals, it is not necessarily because they naturally have better eyes or noses for profits than do others, or because they can somehow sense the future whereas others cannot or do not, or because they persevere in circumstances that would cause lesser souls to give up. It is because, by virtue of their experience in the social world around them, they can see what needs to be done in the present, and, by virtue of the connections that they establish in the social world around them, they are able to do it. Of course, some entrepreneurial successes may be due primarily to dumb luck, but only rarely do people succeed at complex tasks if their decision-making is erratic or based consistently on faulty presuppositions.

Lavoie declines to talk about entrepreneurial vision, spirit, and drive because, in his view, these perceived qualities of persons or minds do not get things done. These terms are not descriptions of entrepreneurial actions. They are individualizing

post hoc explanations, and not very enlightening. Vision, spirit, and drive – whatever they may be meant to indicate – do not accomplish emergent economic, organizational, and technological objectives or bring to completion the development and marketing of new goods and services. Concrete entrepreneurial work has to be done in order to achieve these ends, and this work is always social in character. It is conducted on social fields of cooperation and conflict. It involves communicating ideas, recruiting allies, making commitments, fighting political battles, and negotiating compromises. In this way, it is no different than any other kind of organizational work. Entrepreneurial action is not mysterious or extraordinary. It is ordinary social action, and it can be readily understood. The way to understand it is plain. Once the idea that entrepreneurship is 'embedded' in culture and social processes is accepted as a conceptual guide for research, then actual empirical instances of entrepreneurship begin to cry out for historical and ethnographic description. In the study of entrepreneurship, ethnographies and historical narratives can lend concrete substance to otherwise occult phrases like 'entrepreneurial vision,' 'entrepreneurial spirit,' and 'entrepreneurial drive.'

The same is true of properly sociological concepts like 'entrepreneurial leadership.' Schumpeter, for one, understood leadership to be a central component of the entrepreneurial function.[54] What entrepreneurs do, in his view, is show others the way to technical and social innovations. This is a distinctly sociological conceptualization. Leadership (of any sort) is a constitutively social and

[54] See Joseph A. Schumpeter, "The Creative Response in Economic History," ch. 18 in Essays: On Entrepreneurs, Innovations, Business Cycles, and the Evolution of Capitalism, ed. Richard V. Clemence, New Brunswick, NJ: Transaction, 1989.

organizational phenomenon, an interactive accomplishment. This is so because, as a matter of both semantic logic and social grammar, leaders require followers. They must persuade or compel others to cooperate with them, take direction from them, or support them. These are social tasks, and leadership is success in them. It is emergent and relational in character, and so, not adequately understood or described as a personal quality or ability.[55] The question for sociologists to ask, then, about the phenomenon is 'how do leaders lead?' The way to answer this question empirically is to consider instances of leadership in social, cultural, and historical context. In order to understand leadership as a social product, researchers must make sense of it in terms of the social relations that characterize it in specific times and places. They must describe concrete social relations between leaders and followers. They must learn what it means to lead or follow in a given social setting, and what people must know or believe about their circumstances in order to act and be counted as leaders or followers. Lavoie's hemeneutic theory provides conceptual means for treating 'entrepreneurial leadership' sociologically; ethnographic and historical methods are appropriate means of documenting it empirically.

ENTREPRENEURIAL CHARISMA

Charisma is a similar concept sometimes associated with entrepreneurship. It is a form of leadership, and one of the possible answers to explore when researchers ask 'how do entrepreneurs lead?' Following Max Weber's classic writings on the

---

[55] Many academic investigations of leadership have wandered down this blind alley. For a brief review and criticism of the interdisciplinary field of leadership studies, see Jacob Heilbrunn, "Can Leadership Be Studied?" Wilson Quarterly 18, 2, Spring 1994. For an even more scathing assessment, see Benjamin DeMott, "Choice Academic Pork: Inside the Leadership Studies Racket," Harper's Magazine, 1993, December, 61-77.

topic, sociologists generally consider charisma, like other types of leadership, to be a property of social contexts and interactions rather than individuals. They treat it as an organizational phenomenon. On the Weberian view, charisma appears in the world when people follow and obey another because they perceive in their leader special qualities or powers. These perceived qualities or powers serve to legitimate the leader's authority, while inspiring confidence, loyalty, and, if the charisma is sufficiently pure, personal devotion. For disciples and subjects, charisma appears to be embodied in the person of the leader, but Weber emphasized that it inheres in the relationship between leader and followers. The figure of authority may or may not be extraordinary, in fact, but what matters is that followers believe it to be so. If they believe, they are duty-bound to follow and obey, and as long as they do, the charismatic figure retains authority.

In Weber's analysis of types of legitimate authority, charisma is a residual category used to classify emotional attachments and moral or ideological commitments when found at the heart of relations of authority. It is Weber's default explanation for instances in which people voluntarily obey the commands of a leader but are not obliged by custom or law to do so (and maybe are even forbidden by custom or law to do so). The concept may have some utility in accounting for the 'non-rational' aspects of entrepreneurship and entrepreneurial organizations. Entrepreneurship is creative and innovative. It does not conform to any established pattern of action, at least not wholly, and the specific innovative activities that distinguish it from other forms of action are not bound by any set of formal rules. To this extent, it appears that entrepreneurial venturing displays the hallmarks of

charismatic leadership, and has a place in Weber's typology. Strictly speaking, however, entrepreneurial leadership is not charismatic, because, in order to achieve success, entrepreneurs must establish stable, materially productive organizations. True charismatics, as Weber conceptualized them, do not. According to Weber, charisma "is not an 'institutional' and permanent structure, but rather, where its pure form is at work, it is the very opposite of the institutionally permanent."[56] Entrepreneurs are preoccupied with worldly things, with conducting business; Weber's charismatic leaders cannot be: "the master as well as his followers and disciples must stand outside the ties of this world, outside of routine occupations...."[57] Entrepreneurs pursue profits, but Weber maintains that charisma, in its 'pure' form, "is never a source of private gain for its holders in the sense of economic exploitation by the making of a deal."[58]

Weber's charisma is revolutionary. It serves as the foundation for fundamental transformations in social order. Entrepreneurs are not revolutionaries. Rather, they are creators. They build organizations, businesses. They do not necessarily spark 'paradigm shifts' in patterns of fundamental thought or action. Their work is different in character than that of discoverers, inventors, or political radicals who battle to have unorthodox ideas accepted within scientific disciplines, established industries, or firmly institutionalized social structures. Entrepreneurs usually don't have to wrest

---

[56] Max Weber, "The Sociology of Charismatic Authority," pp. 245-252 in From Max Weber, eds. H.H. Gerth and C. Wright Mills, New York: Oxford University Press, 1946; p.248.

[57] Weber, "The Sociology of Charismatic Authority," p. 248.

[58] Weber, "The Sociology of Charismatic Authority," p. 247.

power and control from the hands of others. They usually don't have to change hearts and minds in order to win them. Typically, it is sufficient for them to make appeals to material and ideal interests that people already hold. It is enough for entrepreneurs, usually, to convince investors and collaborators that if they lend their support and assistance, the project will be successful, new opportunities will subsequently open up, and everyone will make a lot of money. This is the work of the shrewd politician, organizer, or businessperson, not the charismatic revolutionary.[59] Revolutionary activity entails not only persuading people to start doing new things, but also convincing them to abandon old ways, and to embrace new values and ideals. People who attempt this sort of thing often run up against concerted opposition as well as inertial resistance, and they often have to resort to extraordinary moral or emotional appeals to rally the troops. Entrepreneurs generally try to avoid conflicts, because, for them, there's not likely to be profit in it, and when they take time off from pragmatic deal-making to dabble in ideology and rhetoric, their strategies are usually more conventional and subdued.

The biotechnology industry has not made a lot of 'great men' (or women). It doesn't have a mesmerizing champion to represent it or a single grand personage to symbolize its mission. It is populated by intelligent, knowledgeable, and skillful people, many of whom can claim impressive achievements, but the industry's innovative organizational forms are not products of individual will or charismatic

---

[59] Entrepreneurs usually have little interest in challenging power. Typically, they court power. In order to be successful, they usually have to convince wealthy individuals and/or big, powerful institutions (or their agents, at least) to let go of large sums of money. The degrees of difficulty that characterize this maneuver vary, but only rarely is it easy.

subversion. They emerged more by accident than by design, as novel recombinations of preexisting organizational models and customs. Without minimizing the accomplishments of biotech entrepreneurs, if one wishes to celebrate entrepreneurial heroes, perhaps the place to find them on the passing scene is not in start-up companies but rather within large, firmly entrenched bureaucratic organizations. Prospects for attempts to decentralize bureaucratic operations and reconstruct ossified chains of command are enhanced if the clerks believe that the reformer can work magic or is destined for greatness. Biotech entrepreneurs have created new organizations in empty spaces. This is no mean feat, but it doesn't necessarily require extraordinary powers. Reforming a bureaucracy is perhaps the more difficult task, and the greater test of a leader's charisma. Moreover, directing a biotech start-up calls for few awe-inspiring deeds. A lot of time is spent on the telephone. It may be exciting, sometimes, and it may earn admiration and respect, but it doesn't provide many opportunities for displaying one's heroism or supernatural gifts. Much of the day-to-day business of running a biotech company involves measuring hazards and calculating risks to the extent that time and money will permit. It isn't glamorous. It's chancy, to be sure, but while biotech entrepreneurs put huge sums of money in harm's way, the more daring risk-takers by far in terms of personal livelihood are small business people across the country, people without much money or power who mortgage their homes, their families, and their futures for a shot at self-employment.

Biotech entrepreneurs cannot be classified as pure charismatics, but the concept may still have some utility for understanding the ways in which they do their work and accomplish their ends. Weber's categories represented ideal types, and he

cautioned that, in practice, examples of pure forms of traditional, legal-rational, or charismatic authority would be unusual.[60] Most empirical examples of authority or leadership combine elements of the three types in varying proportions, and because charisma is antithetical to custom and law, it struggles constantly against dilution and degradation by countervailing organizational and institutional forces. Emotional and ideal ties to modern leaders and modern institutions tend to be relatively weak, in part because the formation of charismatic movements is inhibited by the remarkable size, strength, and stability of bureaucratized social orders, and when charisma does erupt in this kind of social milieu it is usually tamed and 'routinized' before the rule of law and convention has been threatened. "In the long run," Weber explains, "the continuity of professional operations is tactically superior to emotional worship. Only extraordinary conditions can bring about the triumph of charisma over organization."[61] Weber suggests that, most of the time, charisma will be of limited explanatory value when considering the constitution of modern social order. Still, scholars in science studies have proposed lately that potent forms of charisma survive in contemporary settings, including institutions that, on the surface of things, might be assumed to be among the most rationalized spheres of modern social life – namely, science and technology. They liken scientific and technological projects to charismatic orders, and

---

[60] Max Weber, Economy and Society, Vol. 1, eds. Guenther Roth and Claus Wittich, Berkeley, CA: University of California Press, 1978; p. 216.

[61] Max Weber, Economy and Society, Vol. 2, eds. Guenther Roth and Claus Wittich, Berkeley, CA: University of California Press, 1978; p. 1132.

argue that the spirit of inquiry, innovation, and progress can be (and, perhaps, must be, to some extent) embodied in the person of an extraordinary leader.[62]

Perhaps they are right. If so, the value of the concept of charisma as an interpretive guide in the study of the biotechnology industry lies with the manner in which it draws attention to individual personalities, and the ways in which personalities figure in the constitution, maintenance, and transformation of social order. On the Weberian view, charisma is a property of social relations, so it would be wrong-headed to elaborate the concept by cataloguing the 'special' characteristics of charismatic leaders that elicit fealty and obedience. However, attributing 'special qualities' to particular persons engaged in entrepreneurial activities in particular instances is not the same as claiming that these qualities are essential, defining features of 'the entrepreneur,' or of entrepreneurial leadership. Further, making attributions of this kind when persons appear, in fact, to possess notable traits or styles, or when they are said by others to possess them, can be a useful means of explaining, in part, the histories of entrepreneurial enterprises or entrepreneurial cultures.

Entrepreneurial leaders may well exhibit distinctive personal characteristics that figure in the success (or failure) of the innovative organizational work that they undertake. Acknowledging the fact need not stand as an endorsement of

---

[62] Donald MacKenzie tells how Seymour Cray's personal mystique contributed to technological successes in the supercomputer business. See Donald MacKenzie (with Boelie Elzen), "The Charismatic Engineer," ch. 6 in Knowing Machines: Essays on Technical Change, Cambridge, MA: MIT Press, 1996. Charles Thorpe and Steven Shapin nominate the presence of J. Robert Oppenheimer, the scientific director of the Manhattan Project's Los Alamos laboratories, as an exceptionally powerful organizational and political force embodied in a person. See Charles Thorpe and Steven Shapin, "Who

psychologism or individualism. Individuals in positions of authority will naturally adopt personalized approaches to their work, and when they manage consistently to lead, to create and sustain an organization, or to improve the performance of an organization, their leadership styles may have a lot to do with their success. These styles can appear to be associated with fixed psychological predispositions or elements of personality, but they can also be interpreted as products of definite times and places, of social processes that define structures of authority, and of relationships among persons and groups within these social structures. In other words, it is not individual qualities, per se, that make the difference, but individual qualities as they are shaped by, and as they take on significance within, specific social and historical contexts. Leadership and charisma (like identity, or any other relational social quality of an individual) result from a match between the person and the demands of the moment as their forms are negotiated in social processes.

Of course, circumstances and historical and cultural particularities dictate ranges of possible expressions of charisma. Charisma is marked empirically by the obedience and devotion of subjects. The strength of followers' commitments may vary in intensity and kind, depending on social conditions and expectations. An ecstatic seizure that served as evidence of the Nordic berserk's extraordinary gifts (to borrow one of Weber's examples) would not likely command much allegiance or compliance in San Diego today, and little of the difference in reception could be put down to the quality of the demonstration. By contrast, an archetypal modern

---

Was J. Robert Oppenheimer? Charisma and Complex Organization," Social Studies of Science, 30, 4, 2000: 545-590.

charismatic is perhaps the solicitous boss for whom affectionate employees vow they would 'climb mountains' or 'walk over hot coals.' They likely wouldn't, of course, without the offer of a raise first, but statements of this kind, if genuine, indicate a measure of devotion to the person that extends beyond the call of duty as specified by convention or job description. The qualities that endear managers to subordinates are real organizational forces.[63] They are not just incidental, and because they elicit emotional attachments, they can be classed as charismatic dimensions of the official's authority. But under ordinary conditions in large, bureaucratized corporate structures, this kind of feeling for the boss may exhaust the possibilities for charismatic leadership.

In any case, whenever and wherever charisma appears in particular instances, personal qualities (and social actions expressing them) are important. It is probably safe to assert that, in order to lead effectively, a person must be perceived, minimally, as capable and up to the challenge, whatever that might entail in particular instances. Beyond this, a broad range of personality profiles or leadership styles might be counted as charismatic under the right circumstances. One effective leader might be bold, arrogant, and confrontational; another might be equally effective by playing gentle, humble, and charming. One might be admired for displaying exuberance, intensity, and drive; another might impress by remaining calm, cool, and collected. Brash, colorful, and audacious might work for some; reserved, dignified and restrained

---

[63] See Carol A. Heimer, "Doing Your Job And Helping Your Friends: Universalistic Norms about Obligations to Particular Others in Networks," pp. 143-164 in Networks and Organizations: Structure, Form, and Action, eds. Nitin Nohria and Robert G. Eccles, Boston: Harvard Business School Press, 1992.

might better suit others. Applying adjectives of this sort may be useful for describing persons and individual entrepreneurs, but, obviously, none of the qualities or traits that they represent can count as essential, categorical elements of charismatic leadership because their opposite numbers can produce the same results. Apart from the general theoretical definition that specifies a kind of relation between leaders and followers, not much more can be said about charisma. People know it when they see it, or, at least, some do, sometimes. And they can try to describe it, but they can't really pin down its source or essence. There is something ineffable about it.

In biotech entrepreneurs, charisma might be expressed in a firm handshake, an easy smile, a certain look in the eye, or a knack for telling a good story about a technology on which they hold a patent or a license. Entrepreneurs may require at least some qualities of this kind in order to inspire the confidence of others in themselves and their projects. Becoming a biotech entrepreneur, a person who knows how to get things done in this milieu, involves learning the science, learning the business, and learning how to affect the manners that will smooth flows of vital resources to the right places at the right times. It involves developing a personal style appropriate to the context, and it may involve cultivating a bit of charisma to win people over to one's side. This kind of entrepreneurial charisma is dispersed throughout the industry – a little bit of it here, in this person, a bit more of it over there, next door, in that person. It appears to be embodied in many different persons, in many different ways, in many different situations.

The concept of charisma may serve in another way as a useful interpretive resource in the study of biotechnology. Just as it may be worthwhile to think of

entrepreneurship as a fundamentally social phenomenon, consisting in communication, networking, and cooperative labor, it might be worthwhile to consider entrepreneurial charisma as a phenomenon generated and distributed in the same manner. Innovative organizations and industries can be called entrepreneurial. There might be organizations and industries that can be called charismatic, as well. If so, biotech companies and the biotech industry certainly fit the bill. Firms in the biotech industry have generated enthusiasm, incited passion, and engendered loyalty among scientists, post-docs, students, teachers, investors, stock market analysts, physicians, patients, and politicians, among others, and sometimes even when, on close inspection of the scientific record, no rational basis for such reactions can be found.

In cases of high-tech charisma, it appears that it is often not the person that is special, but rather the group, the team, the organization, the company, the time and the place, or the exciting task of surfing on the leading edge of technological progress, developing new tools or products that may be, not only valuable commodities, but also beneficial gifts to humankind. When the stakes are high, when success or failure means so much to so many, when progress involves going places that no one has ever been before, and when the pace of the industry demands a constant and unrelenting 'sense of urgency,' teams may share a special spirit of camaraderie when they make discoveries or bring projects to completion. Entire companies may adopt a swagger when they're winning and ahead of the pack, and if they're working to develop cures for cancer or Alzheimer's disease, those within may experience a genuine sense of common purpose or mission. The atmosphere around the industry as a whole may be thick from time to time with anticipation. When a competitive race for an important

technical milestone heats up, for instance, excitement grows, and journalists and investors assemble as spectators to witness the drama as it unfolds.

The charisma of biotechnology may be experienced, sometimes, as an extraordinary 'buzz in the air.' Many participants in the field have commented on this feeling and tried to name it. It resembles what Weber called "office charisma" – "the belief in the specific state of grace of a social institution."[64] This is a form of 'depersonalized' and 'routinized' charisma. According to Weber, charisma is, by nature, unstable, evanescent, and fleeting. In every case, it is "on the road from a turbulently emotional life that knows no economic rationality to a slow death by suffocation under the weight of material interests."[65] Despite this inevitability, the disciples of a charismatic leader usually wish to prolong the movement beyond its natural time, and, to this end, may arrange for an orderly succession of authority through inheritance, ordination, anointment, acclamation, or plutocratic acquisition. The followers move to 'routinize' and institutionalize the authority once embodied in the person of the leader. In this way, says Weber, "the charismatic following of a war leader may be transformed into a state, the charismatic community of a prophet, artist, philosopher, ethical or scientific innovator may become a church, sect, academy, or school...."[66]

Charismatic authority becomes depersonalized in these processes because it no longer resides with the special powers of the leader, but is instead invested in the

---

[64] Weber, Economy and Society, Vol. 2, p. 1140.

[65] Weber, Economy and Society, Vol. 2, p. 1120.

[66] Weber, Economy and Society, Vol. 2, p. 1121.

institution that grants it to qualified holders. In modern social organizations that differentiate between the office and the incumbent, this depersonalization reaches its fullest expression. Modern patriotism is a phenomenon that exemplifies it. Love of country, for some, may be deeply emotional and fervently felt, and citizens may respect and even revere the authority residing in the offices of the government. At the same time, however, and without questioning the integrity of the state and its organs, they may mistrust its officials, and regard the motives and interests of these individuals with profound cynicism. In such cases, the charisma that commands allegiance is perceived by subjects to be embodied wholly in the office, in the social institution, and not in the person. A force of this kind appears to be evident in the biotech industry. Biotech entrepreneurs and biotech companies trade heavily on (but also contribute to) the institutional charisma of the sciences.

Since the scientific revolution in the 17th century, modern people in the West have, by and large, embraced the idea of 'science' as a special form of inquiry and an institutional repository of privileged bodies of knowledge. The aura surrounding the social institution of science is bound up with ideas expressed in modern philosophical accounts of 'scientific method.' These accounts portray processes of scientific inquiry as 'disinterested' and 'objective,' i.e., as impersonal. The special method so described is often said, not only by philosophers, but by scientists themselves, to distinguish science as an institution and to account for its success in accumulating useful knowledge and gradually revealing the truth about the natural world. As sociologists and historians of science have pointed out, if this view of method is taken seriously, then the personal qualities and interests of individual scientists can be dismissed as

inconsequential, or worse, as sources of possible bias or fraud.[67] This 'rationalized' view of science has served to depersonalize the charisma of the institution.[68]

Another factor contributing to the confidence of moderns in science as an institution is the astounding practical success that has been achieved by scientists working in many disparate fields of inquiry. Just like the great war chieftain who must continually prove himself with glorious victories in battles, if science is to maintain its authority and privileged social standing, it must continually make progress and deliver booty to the rest of the tribe. So far, it has acquitted itself spectacularly on many different fronts, and there is every expectation in the culture at large that it will continue to prove its worth. In the modern world, faith in science is strong. This faith is based on a kind of charisma that is perceived to emanate from the institution itself. Many biotech entrepreneurs have put it to use and made it their own, and the biotech industry shares in the glory. Few biotech scientists or entrepreneurs are publicly known by name, but the idea is widespread that, as a group, they are employing special tools for special purposes.

---

[67] For 'Kuhnian' historical and sociological views on science and method, see H.M. Collins and Trevor Pinch, The Golem: What Everyone Should Know About Science, Cambridge: Cambridge University Press, 1993; Thomas S. Kuhn, The Structure of Scientific Revolutions, Chicago: University of Chicago Press, 1970 [1962]; and Steven Shapin, The Scientific Revolution, Chicago: University of Chicago Press, 1996.

[68] Not included among prominent modern stereotypes regarding scientists and engineers are portraits of charismatic heroes. They do include, though, the 'mad scientist' anti-hero and the socially incompetent egghead or nerd. These are not images of persons who are likely to inspire trust or confidence, but beliefs in the power of science and engineering remain firm throughout the culture, nonetheless. Even more telling are representations of 'Big Science' technicians as cold, purely analytical and dispassionate, anonymous white lab jackets, automatons slavishly and systematically following procedures and deriving facts according to strict rules of evidence and inference. Here, progress moves steadily ahead even though real people have vanished from the scene, replaced by workers who resemble robots more than human beings.

This depersonalized form of charisma doesn't have to be embodied in prophets, sorcerers, fearless warriors, or spellbinding orators. It is dispersed across and embedded in the interactions that constitute and animate the biotechnology industry, and it is simultaneously localized in the geographic regions that serve as centers of biotech development. This kind of charisma, just like the pure form embodied in the one extraordinary individual, is an emergent and relational social phenomenon. And just like the varied human and material resources that circulate through the connections, associations, and alliances that hold the field together, it is 'networked' and 'concentrated.' Its movements and accumulations can be mapped by charting flows of people, information, capital, the attention of Wall Street, and so on, in, around, and through the various precincts of the industry. It is, in fact, a property of these flows. And its effects are evident as the innovative forms of organization and patterns of action that characterize the biotech industry.

SCIENTIFIC ENTREPRENEURSHIP IN SAN DIEGO

The associations, connections, and intersecting social processes that have combined to produce the 'enchanted' bustle and ferment of biotechnology are innumerable. The phenomenon of scientific entrepreneurship and its circumstances in time and space can be astonishingly complex. To begin to understand it, researchers are obliged to move from the identification of simple cause and effect relationships to 'thick descriptions.' Historical and ethnographic methods are required because the social processes in which entrepreneurs act are rife with contingencies. Outcomes in particular cases are always dependent on how individuals and groups move concretely through entrepreneurial processes, monitoring environments, accumulating

experience, making decisions that are never perfectly informed, and sometimes, making mistakes and guessing wrong. Those starting new enterprises usually have to amend, revise, and correct their plans, and, in some cases, they have to start over from scratch. Sometimes what entrepreneurs end up accomplishing hardly resembles what they originally set out to do, and sometimes the consequences of their actions are mostly unintended. Entrepreneurial discovery is a process that spans careers and takes shapes concretely by passing through countless situations and locales in which people interact and exchange information and resources. If understanding the emergence or development of innovative enterprises is the goal, then researchers ought to pay close historical and ethnographic attention to the entrepreneurial process in social context.

This is not to say, as demand side theorists seem to imply, that credit and blame are not rightly assigned to individual entrepreneurs or groups of entrepreneurs, and are instead properly attributed to culture, social structure, market conditions, or something else. It simply means that ethnographic and historical research on entrepreneurs and entrepreneurship in context can provide richer understandings than explanatory variable analysis. These modes of inquiry can bring to light aspects of entrepreneurship that are often neglected in analyses that rely on 'extrinsic' factors to explain entrepreneurial behaviors and new forms of enterprise. If the entrepreneurial process is comprised of situated, context-bound innovative actions, then descriptions of these actions and histories of the innovators who carry them out will show what the phenomenon of entrepreneurship is.

This dissertation offers histories of entrepreneurial careers and descriptions of entrepreneurial work in specific social and historical contexts – those relevant to the

emergence of the biotechnology in San Diego. Since these histories and descriptions speak for themselves, I have no precise definition of entrepreneurship to offer. Instead of trying to pin down the essence of entrepreneurship, I borrow Thornton's appropriately vague formulation – she calls entrepreneurship "the creation of new organizations, which occurs as a context-dependent, social and economic process."[69] This is a properly sociological definition. By focusing on organization building, it emphasizes the collective aspects of entrepreneurship. Entrepreneurs always act as entrepreneurs within definite social contexts, that is, always in relation to others, and in response to complex and dynamic social conditions. Attempts to describe, analyze, and understand entrepreneurship by focusing narrowly on the decisions and actions of individuals – as economists and psychologists are wont to do – are, from a sociological perspective, lacking in depth. Similarly lacking are attempts to describe, analyze, and understand entrepreneurship as a function of structural conditions and demands. Without discounting the degrees of freedom that individuals may exercise voluntarily, or the constraints that circumstances may impose on individuals, social histories of entrepreneurship can show how the character and sense of entrepreneurial decisions and actions are always bound to concrete social situations and contexts.

In this study of San Diego biotechnology, I follow Thornton's lead and use the term 'scientific entrepreneurship' to indicate all that starting and directing a small science-driven company entails. Naturally, this encompasses tasks so manifold and complex that the phenomenon of bioentrepreneurship cannot be coherently rendered

---

[69] Patricia H. Thornton, "The Sociology of Entrepreneurship," Annual Review of Sociology 25, 1999: 19-46.

as anything but a collective and socially distributed process. In fact, as Schumpeter knew well, so thoroughly social is the entrepreneurial function that identifying individual entrepreneurs becomes conceptually problematic: "In many cases," said Schumpeter, "it is difficult or even impossible to name an individual that acts as 'the entrepreneur' in a concern. The leading people in particular, those who carry the titles of president or chairman of the board, may be mere co-ordinators or figureheads."[70] Schumpeter points out that individuals play roles and make contributions to entrepreneurial projects – and descriptions of these projects can shed light on just what these roles and contributions are – but, of course, only rarely, if ever, can individuals claim to have single-handedly effected change in the direction of a collective social process. The Hybritech story illustrates Schumpeter's points. When examining the formation of Hybritech and its begattings, it is often difficult to identify 'the entrepreneur.' It is possible, however, to identify many of the unique contributions that individuals and groups made to the founding and maturation of Hybritech, and later to the formation of the larger biotech industry in San Diego.

When successful entrepreneurial projects came to fruition in San Diego's biotechnology industry, they did so because many people worked together. As these people cooperated in order to make technological and organizational innovations, their personalities, backgrounds, values, talents, skills, work habits, and judgments all mattered. They are all part of this scientific, technological, and economic story. British business historian Charles Wilson has remarked, "at the heart of the economic

[70] Joseph A. Schumpeter, "Economic Theory and Entrepreneurial History," p. 261.

process there is human intelligence, human character, ingenuity and enterprise."[71] The same can be said, of course, of scientific inquiry, and of the marriage of basic science and commerce in the development and application of biotechnologies. These dimensions of innovation are often lost or obscured in academic analyses of biotechnology that speak in abstract terms about dollars, markets, factors of production, networks, and so on. This study aims to retrieve them.

[71] Charles Wilson, The History of Unilever: A Study in Economic Growth and Social Change, London: Cassel, 1954.

IV. "TECHNOLOGY'S PERFECT CLIMATE"

> Revolutions are not made; they come. A revolution is as natural a growth as an oak. It comes out of the past. Its foundations are laid far back.
>
> Wendell Phillips

PLACE MATTERS

When it comes to technological change, place matters.[1] People invent, and individuals and groups design and manufacture, but technological artifacts appear in their own places, and in their own good time, naturally. Contextualizing historians tell us that particular locales may be more or less conducive to technological development and 'progress.' Each invention has it own set of requirements that must be met before it makes an appearance, its own set of necessary causes that must precede it. The likelihood that any given place and time will witness an invention depends on many different factors – social, cultural, economic, and political, as well as technical. Certain conditions may prevent the creation or adoption of a new technology, while certain others may open historical windows for innovation and change.

Sometimes techniques or artifacts can only be implemented at the sites in which they are brought into the world. In other instances, techniques or artifacts originating in one place must be transported to others before they are able to flourish,

[1] This idea is contrary to the notion that 'distance is dead' in the age of infotech. See "Place Matters," The Economist, November 9, 2000; and Joel Kotkin, The New Geography: How the Digital Revolution is Reshaping the American Landscape, New York: Random House, 2001.

before their historical impacts and potential benefits or costs are fully realized.[2] Technological changes can be usefully traced by historians, not only through time, but through social and geographic spaces, as well. For contextualists, technologies are bound to chains of concrete events in the world, to definite circumstances, definite places, and definite passages between them. Histories of technologies are sometimes best related, not just as evolutionary transformations in design, but also as travelogues. Technologies may sometimes have to travel considerable distances along circuitous routes to find their places. They may have to bounce around a good bit, following uncertain paths, until they intersect, sometimes very unexpectedly, with other historical chains of events that lead them home. Technologies are invented, adopted, or utilized at temporal and geographic points where histories of artifacts and ideas, histories of peoples and cultures, and histories of locales all converge to make particular places the right ones. Places matter, too, in technological development, and

[2] In a book called The Pinball Effect, popular historian James Burke offers the example of an agricultural innovation introduced to England in the early 18th century, by a gentleman named Jethro Tull. In 1713, during a stay in the south of France, Tull observed that when local winegrowers used ploughs to deep-hoe between their vines, they didn't have to use manure to fertilize their soils. He took the idea back with him to England and found that he got similar results with turnips, potatoes, and wheat, and that his crop yields were greatly improved, to boot. In 1733, Tull wrote a book about his experiments, The Horse-Hoeing Husbandry. After the book was translated into French and discovered by francophone English landholders, deep-hoeing by plough was widely adopted throughout the land. Burke relates that deep-hoeing, in conjunction with the similarly new practices of crop rotation and the enclosure of farm lands and pastures, contributed significantly to England's 18th century economic ascendance. Advances in agricultural production during the period led to more food, cheaper prices, an increasing population, vast expansions of markets, urbanization, and, in short order, the Industrial Revolution. He also notes that hoeing did not have the same beneficial effect on French agriculture and industry because of the particular conditions in France at the time: the "appalling state" of roads in the country, the stubborn preservation of feudal property rights that discouraged capital investments, and an uncoordinated system of different regional weights, measures, and levies. All of this, and more, prevented the French from developing a national market on the same scale as their neighbors across the channel. While English agriculture and economic activity rapidly grew, French farming and commerce remained constricted and disorganized by comparison. Deep-hoeing had first been developed in France, but its economic benefits could not be fully realized in its native land. James Burke, The Pinball Effect, London: London Writers, Ltd., 1996.

if a place is to foster technical innovations, it must be prepared to do so, by design, by accident, or a little of both.

Many things had to happen in San Diego, and elsewhere, in order for the biotechnology industry to emerge in the city in the way that it did. Of course, San Diego's universities and research institutions had first to be established, and then new techniques in the life sciences and biomedicine had to arrive, along with venture capital and entrepreneurial scientists. These local happenings were naturally impacted and shaped by historical processes unfolding on larger scales. Broader trends leading up to the formation of the new 'global' economy – the growth of academic and industrial research, the expansion of government support of basic science in the U.S., the maturation of financial communities and markets, and evolving conditions in legal and commercial environments in the U.S and around the world – all influenced the development of biotechnologies in San Diego. But before any of these influences could work on events taking place in the city and surrounding areas, there had to be a place called San Diego, a place that could attract, nurture, and sustain scientific progress and high-tech industries. San Diego's first bioentrepreneurs appeared in the 1970s on a stage set by the region's long and unique natural and social histories.

"TECHNOLOGY'S PERFECT CLIMATE"

Many people who visit the city of San Diego are enchanted by it. Located in the far southwest corner of California and the continental United States, it is a hospitable place, blessed with abundant natural beauty. The downtown area fronts a picturesque harbor. The commercial and residential districts surrounding the urban center are nestled among pleasantly undulating hills of the kind peculiar to Southern

California's quirky earthquake-generated topology. On clear days – and most days are clear in San Diego – high places around the city offer sweeping views of the local environs, the ocean, and the mountain ranges that lie to the north and east. The landscape does not always make for convenient travel. Many streets come to abrupt dead-ends where canyon walls suddenly drop hundreds of feet, and motorists shuttling between adjacent sections of town must often follow circuitous, time-consuming routes in order to reach their destinations. But the irregular geography of the place makes for wonderful scenery. As cities go, San Diego is an unusually pretty one.

Perfection is a word often used to describe the agreeable climate of the region.[3] San Diego, it is said, has the shortest thermometer in the United States. Nowhere in the country is the weather more consistent or consistently pleasant. Rarely do temperatures rise above 80° F during the day, or drop below 50° F at night. High temperatures in the summer months average 75° F. In January, the coolest month, highs average 66° F. Only eleven times since the federal government started keeping track in 1849 have freezing temperatures been recorded in the city. Snowflakes were last reported in 1937. Even in the winter months, dry Santa Ana winds regularly blow in from the Mojave Desert to the northeast, causing the mercury to rise and residents to shed their sweatshirts and jackets.[4] In San Diego, it is often difficult to tell the

---

[3] For a meteorological analysis, see Thomas E. Evans, III and Donald A. Halvorson, "Climate of San Diego, California," NOAA Technical Memorandum, NWS WR-256, Springfield, VA: National Technical Information Service, U.S. Dept. of Commerce, October 1998.

[4] Santa Ana winds originate from the Great Basin High, a relatively stable, clockwise flow of air centered over Nevada and Utah. The High is trapped between the Sierra Nevada to the west and the Rocky Mountains to the east. When low pressure centers take up residence along the Pacific coast, the hot, dry desert air is then drawn through mountain passes to Southern California. See Arthur G. Lessard, "The Santa Ana Winds of Southern California," Weatherwise, 1988, 41: 100-104.

season by the weather. A better indicator is the vegetation on the city's hillsides. When spring arrives at the end of the winter rainy season (inhabitants of Northern California's temperate rain forests scoff at the suggestion that San Diego has a rainy season) freeway commuters zoom past emerald escarpments. By midsummer, the palette is muted; the hillsides are parched and brown.

Less than ten inches of precipitation fall on San Diego in a typical year, almost all of it during the winter months. Due to its latitude, the city is rarely visited by the storm systems that move across the North Pacific, or by the tropical depressions that spin regularly into central Mexico. Thunderstorms are almost unknown. On average, only three occur per year, and most quickly dissipate. San Diego mornings are often shrouded in fog (what local meteorologists call the 'marine layer'), but this usually burns away by midday to reveal clear blue skies. Only when Catalina Eddy conditions are present offshore does the fog linger.[5] This happens most often in June. When it does, San Diegans call it 'June gloom.' Yet, normal rainfall for the month of June is less than one-tenth of an inch. It almost never rains in the summertime. City residents schedule summer outings without contingency plans. Travel brochures that advertise the unique charms of the city's climate do not lie. In 1888, General A.W. Greely, head of the United States Weather Service, remarked:

> The American public is familiar on all sides with elaborate and detailed statements on the weather at a thousand and one resorts. If we may believe all we read in such reports, the temperature never reaches the

[5] A Catalina Eddy forms when strong winds blowing in from Point Conception above Santa Barbara run into the Southern California coastline and moist air begins to circulate in a counterclockwise direction around a low pressure center in the vicinity of Catalina Island, situated about 25 miles due west of Laguna Beach. See Kyozo Ueyoshi and John O. Roads, "Simulation and Prediction of the Catalina Eddy," Monthly Weather Review, 1993, 121: 2975-3000.

> eighties, the sky is flecked with just enough clouds to perfect the landscape, the breezes are always balmy, and the nights ever cool. There is possibly one place in the United States where such conditions obtain: a bit of country about forty miles square, at the extreme southwestern part of the United States, in which San Diego, California is located.[6]

Because of its attractive climate and seaside location, San Diego can count on tourism as a stable component of its economic base. According to a study commissioned by the San Diego Association of Governments, the tourism industry employs more San Diegans (over 65,000 in 1996) than any other economic sector.[7] Visitors flock to this congenial place in droves. For many Americans, and for others around the world, the name San Diego conjures up images of palm trees, sunshine, and sand. The city's legendary beaches are the principal draw. Each has its own unique character and clientele. Each attracts a different mix of locals and tourists, young people and old, sunworshippers, swimmers, scuba divers, and surfers. The warm ocean temperatures provide inviting opportunities for water sports of all kinds.[8] Naturalists are also drawn to San Diego's coastal areas. The western edge of the city stretches for thirty-five miles along the cliffs, coves, caves, tidepools, and salt marshes of the California Coast.

---

[6] Quoted in Evans and Halvorson, "Climate of San Diego, California," p. 16.

[7] San Diego Regional Technology Alliance, Industrial Clusters in the San Diego Region, San Diego, CA: San Diego Regional Technology Alliance/SANDAG, n.d.

[8] For many well-to-do residents of the city, including a few bioindustrialists, sailing is a convenient get-away activity. On clear days, the blue waters in and around San Diego harbor are usually decorated by dozens of small white sails. Occasionally, pleasure craft must dodge huge aircraft carriers and other large naval vessels barreling into port from duty around the Pacific, but the balmy weather makes San Diego a sailor's paradise. In recent years, the city has become a familiar destination for members of the international sailing community. Four times in the 1980s and 1990s, yachtsman Dennis Conner skippered sloops to victory in America's Cup challenges, bringing the trophy and challenge races home

The consistency and mildness of the weather found along the coast stands in marked contrast to the variable and sometimes extreme conditions encountered inland to the east. Beyond the city limits lies the rest of San Diego County, one of the largest counties in the land. It covers 4,255 square miles, more than the states of Delaware and Rhode Island combined. Few places in the world offer the variety of natural environments found within this territory. Above the ten to twenty mile-wide coastal terrace, where most county residents make their homes, inland hills and valleys sweep up toward the six-thousand foot peaks of the Laguna and Cuyamaca mountains. Most of San Diego County is still pristine wilderness, and its highlands are teeming with wildlife.[9]

Many San Diegans appreciate the climactic contrast, the visual beauty, and the recreational opportunities that the mountains provide. On clear winter days, residents of the city can look out to high snow-covered peaks and moraines in the distance. When the crests are white, many who fancy winter activities like tobogganing, snowboarding, and cross-country skiing warm up their cars for the forty-five minute climb to the Sunrise Highway that runs atop the County's highest mountain ridges. When the snows melt early in the spring, the San Diego County highlands become destinations for hikers, campers, boaters, rock climbers, hunters, and trout fishermen. Others ascend to visit the Mt. Laguna Observatory operated by San Diego State

---

to the San Diego Yacht Club. For the title of 'sailing capital of the U.S.,' San Diego now perhaps rivals Newport, Rhode Island.

[9] Mountain lions, for example, thrive in the Lagunas and Cuyamacas as in few other places around the United States. See Kristen Green, "Mountain Lions to be Tracked, Studied/Long-Term Effort to Take Place at Cuyamaca, Anza Borrego," San Diego Union-Tribune, October 31, 2000.

University and Cal Tech's Mt. Palomar Observatory. The Palomar site is home to the monstrous Hale telescope, one the world's largest optical instruments. Situated high above the ambient light of Southern California's cities at 5,500 ft., it is powerful enough to gaze more than a billion light years into the heavens and the past.

Standing atop the steep eastern face of these mountains affords a lookout over the vast Anza-Borrego Desert nearly a mile below. Anza Borrego is part of the lower Colorado Valley portion of the Sonora Desert. The Sonora is the lowest, driest, and hottest of the four North American desert biomes (the others are the Great Basin, Mojave, and Chihuahua deserts). In an average year, only two to three inches of rain fall in this part of the world, but it is enough to make wildflowers bloom like madness on the desert floor from January to March. Millions of years of seismic activity in the region, along the San Jacinto and Elsinore splinter faults of the San Andreas, have pushed up barren mountain ridges that punctuate expansive desert chaparrals and badlands. Few people reside permanently in this desolate place. Borrego Springs, an oasis of spas and resorts, is the largest human settlement in the area, with 3,000 inhabitants. Summer temperatures in Anza Borrego often soar above 120° F. Readings taken from the sun-baked desert surface can exceed 180° F. In the winter months, though, temperatures moderate significantly; conditions in the desert are, for much of the year, tolerable and pleasant.

The quality and variety of the natural environments found in San Diego County have always attracted people, but, of course, the climate and the landscapes are no longer the only draws. As the population of the region has grown, the cultural life of San Diego has naturally blossomed, as well, and become ever more variegated

and colorful. According to the latest U.S. Census Bureau estimates, San Diego has become the second largest city in California, following only Los Angeles,[10] and the sixth largest in the United States. The population within the city limits exceeds 1.2 million. The figure for the larger metropolitan area is approaching 3 million. This makes the San Diego metro area the seventeenth largest in the country.[11] The cultural life of the region naturally reflects the composition as well as the size of the population. Like the rest of California, San Diego features a high degree of racial and ethnic diversity. In 1998, the city's population was 60% white, 24% Hispanic, 9.2% Asian, and 6% African-American.[12] Numerous other ethnic groups, including Native Americans, accounted for the remaining .8%. Many of these communities sustain their own distinctive customs and practices, folding them into the larger patterns that make up daily life in San Diego and its environs.

With this mix of peoples and ways of living, along with the innumerable subcultures and modes of activity that characterize workaday worlds around the city, San Diego residents do not suffer from cultural deprivation of any kind. And, for many (and even those who fancy themselves 'laid back' Californians) life in the city now proceeds at a rapid pace. While in the past, many people came to San Diego in search of peace and quiet, more come now for excitement and stimulation. It is

---

[10] As a metropolitan area and population center, the San Francisco Bay Area, including Oakland, San Jose, and dozens of other towns, is considerably larger According to the 2000 census, the population there now exceeds seven million. This makes the Bay Area the fifth largest concentration of people in the U.S.

[11] U.S. Census Bureau, http://www.census.gov/population/www/Cen2000/phc-t3.html.

[12] San Diego Association of Governments, "San Diego Region Demographic and Economic Characteristics," INFO, March-April, 1999.

possible to sample in San Diego all that big city life has to offer, and many take advantage of the opportunities. When the whistle blows at work, San Diegans, and especially those belonging to the fortunate classes, have plenty of cultural activities and diversions from which to choose. Nothing is lacking.

Eucalyptus-lined boulevards and freeways lead out of the city to the north and south to many other cultural attractions nearby. Just a few miles to the south lies the international border with Mexico, and across it, the federal state of Baja California and the city of Tijuana, now a major urban center with a population exceeding one million. For many San Diegans, Baja California represents a popular travel destination. Tijuana relies heavily on the dollars that visitors bring with them and leave behind. Thousands of sightseers funnel daily through the San Ysidro and Otay Mesa crossing points to shop, dine, and experience a slice of Mexican life.[13] Beyond Tijuana, other popular attractions for visiting Americans include the beach towns of Ensenada and Rosarito, and, to the east, on the Sea of Cortés, the old fishing village of San Felipe. Further south, for more adventurous travelers, the length of the mostly uninhabited Baja Peninsula stretches more than a thousand miles to the resort town of Cabo San Lucas.

---

[13] Visitors usually head directly to Avenida Revolucíon, the city's main thoroughfare, which is lined with restaurants, nightclubs, and scores of small shops. Most avoid exposure to the social and cultural dislocations that characterize life in many other parts of the city. Because of its proximity to the U.S., and especially after NAFTA, Tijuana has attracted both investments in maquiladoras – assembly plants operated by American firms in order to take advantage of relatively cheap Mexican labor – and workers who migrate north from other parts of the country where good employment opportunities are scarce. Tijuana is a city that has grown from a clash of First World wealth and Third World poverty. One observer remarks: "Tijuana boasts some of the highest wages in Mexico, yet few Mexicans are eager to make it their permanent home. For many jobless transplants it is a place of rootlessness and impermanence, of crime and crass commercialism that deplete the soul." See Scott Sernau, Bound: Living in the Globalized World, Bloomfield, CT: Kumarian Press, 2000, p. 75.

Seventy-five miles north of San Diego's city limits lies Orange County, the edge of the urban sprawl that that covers the entire Los Angeles Basin. An area of nearly 1,000 square miles, once known for its pastoral landscapes and citrus groves, as the name suggests, Orange County has now been mostly paved over and covered by strip malls and suburban housing developments. Today, 2.7 million people live in this place. The huge metropolis extending beyond to the north and west features sixteen million people, seemingly endless miles of cloverleafing freeways, and strangely muted sunsets viewed through suspensions of brown and yellow haze. Many civic-minded San Diegans express disdain for what Los Angeles has become. They view their own city as a clean, wholesome, and relatively uncongested place in contrast, and wish to preserve the difference. By and large, they resist 'Los Angelization,' and are ambivalent about development that may compromise the uniqueness of the city, swallow up the countryside and the beach towns that buffer San Diego from its huge neighbor to the north, and bring with it the social and environmental troubles that plague the megacities of the world. Still, San Diego's proximity to Los Angeles is an important part of its identity. The city's economy remains dependent on transportation and financial resources concentrated in the L.A. basin, and most San Diegans, in truth, probably consider convenient access to the metropolis more of a blessing than a curse.

San Diego's climate, landscapes, and cultural resources help to make it a desirable place in which to live. High-tech industries and high-tech people have been attracted to San Diego largely by the quality of life that the city offers them. The weather, the natural environments, and the social composition of the region contribute significantly to it. People have always been drawn to San Diego because it is sunny,

mild, and beautiful. Scientists and engineers are people, too, and, as a group, they appreciate and enjoy comfortable weather, natural beauty, and recreational opportunities as much as any other. Civic leaders attempting to encourage the growth of high-tech innovation and commerce in the city do not underestimate the value of sunshine, scenery, and social vitality as marketing tools. They hope to capitalize on the unique natural and cultural resources with which San Diego has been endowed. The quality of life that San Diego offers is now threatened in many ways by its own social and economic success, but, for the present, the region continues to enchant many of its inhabitants and visitors.[14] In order to attract entrepreneurs, 'think workers,' and new high-tech companies, the San Diego Regional Economic Development Corp. boast that San Diego offers "Technology's Perfect Climate."[15] The phrase refers to the city's business environment and scientific infrastructure as much as it does the weather, but San Diego's rich social, economic, and natural histories have always been intertwined in this way.

OLD TOWN AND NEW TOWN

Anthropologists believe that the area around present day San Diego was first populated by wanderers from the north who settled along the coast, perhaps as early as 20,000 years ago. These people are known today as the San Dieguito, or La Jollans.

---

[14] If San Diego is going to be called heaven on earth, it has to be mentioned, for the sake of truth in advertising, that it also encompasses parts of purgatory and hell. It is an American metropolis, and so, of course, has neighborhoods plagued by costly inner-city social pathologies (e.g., poverty, unemployment, failing schools, inadequate health care, unsafe working conditions, pollution, racial and ethnic conflicts, youth gangs, violence, and high rates of street crimes like robbery, prostitution, gambling, drug abuse, and so on), and in which opportunities for people are lacking. But these 'mean streets' are located mainly in eastern and southern sections of the city. San Diego's extensive freeway system makes it possible for residents living and doing business in other parts of town to avoid them.

[15] Maricris G. Briones, "Target: Prospective Residents," Marketing News, Oct 12, 1998, pp. 1,10.

They lived as gatherers, collecting fruits, vegetables, and nuts, and harvesting mollusks and fish from the sea.[16] Europeans first reached modern day California early in the 16th century, through explorations of the northern end of the Sea of Cortés launched from the Vice-Royalty of New Spain (present-day Mexico and Central America). The discovery of San Diego occurred when the colonial governor of New Spain, Pedro de Alvarado, financed an expedition to investigate unexplored lands along the Pacific coast to the north.[17] He recruited a Portuguese soldier of fortune, Juan Rodríguez Cabrillo, to captain the exploratory voyage. Cabrillo sailed into San Diego Bay under a Spanish flag on September 28, 1542. He called the place San Miguel, misrecorded its latitude, and left, never to return. No white men visited the bay again until November 10, 1602, when Sebastián Vizcaíno came looking for a suitable port from which to dispatch Spanish galleons to the Far East. He renamed the

---

[16] On the histories of native inhabitants in the San Diego region, see Richard L. Carrico, Strangers in a Stolen Land: American Indians in San Diego, 1850-1880, Sacramento, CA: Sierra Oaks, 1987; Leslie Speier, "Southern Diegueño Customs," pp. 297-358 in University of California Publications in American Archaeology and Ethnology, Vol. 20, Berkeley, CA: University of California Press, 1923; Wiliam Sturtevant, ed., The Handbook of North American Indians, Vol.8, California, Washington, D.C.: Smithsonian Institution, 1978; Phillip M. White and Stephen D. Fitt, A Bibliography of the Indians of San Diego County: The Kumeyaay, Diegueño, Luiseño, and Cupeño, Lanham, MD: Scarecrow Press, 1998.

[17] On the modern history of San Diego, see Samuel F. Black, San Diego County, California: A Record of Settlement, Organization, Progress and Achievement, Chicago: S.J. Clarke, 1913; Ed Davidson, San Diego: A Brief History, 1542-1888, San Diego, CA: Arts & Crafts Press, 1929; Carl H. Heilbron, History of San Diego County, San Diego, CA: San Diego Press Club, 1936; Robert Mayer, ed., San Diego: A Chronological & Documentary History, 1535-1976, Dobbs Ferry, NY: Oceana Publications, 1978; Michael McKeever, A Short History of San Diego, San Francisco, CA: Lexikos, 1985; James R. Miller, San Diego: Where California Began, 4th ed., San Diego, CA: San Diego Historical Society, 1976; Irene Phillips, The San Diego Story: 1769-1963: Where California Began, San Diego, CA: South Bay Press, 1963; Richard F. Pourade, The History of San Diego, Vol. 1-7., San Diego, CA: Union-Tribune Publishing Co., 1960-1977; Philip R. Pryde, ed. San Diego: An Introduction to the Region, 3rd ed., Dubuque, IA: Kendall/Hunt, 1992; Shannon, Don, Mission to Metropolis: A History of San Diego, National City, CA: Bayport Press, 1981; Smythe, William E., History of San Diego, 1542-1907, San Diego, CA: The Historical Company, 1908.

place San Diego. Vizcaíno was impressed by the natural harbor, but San Diego remained unsettled by Europeans for another century and a half.

During this time, the Spanish established firm control over Baja (Lower) California, but through the mid-eighteenth century, Alta (Upper) California remained unexplored. In the 1760s, King Carlos III, fearing Russian encroachment on Spanish claims further north along the Pacific Coast, ordered expeditions to map and secure the region. Spaniards finally returned to San Diego in 1769, when Gaspar de Portolá and a small contingent of soldiers arrived to establish a military outpost on what is now called Presidio Hill, a bluff overlooking a floodplain through which the San Diego River travels the final leg of its run from the Laguna Mountains to the sea. Today, this lowland is called Mission Valley. It divides the downtown area of the city from its northern suburbs. Towering freeway bridges span the chasm, and the greenery on the floor of the valley has been replaced by office buildings, apartment complexes, motels, automobile dealerships, and shopping malls.[18]

Portolá was accompanied by a fifty-five year-old Franciscan priest, Father Junípero Serra. Upon his arrival, Serra declared San Diego "a desirable place" and set about the work of establishing the Mission San Diego de Alcalá.[19] The San Diego mission was the first in a chain of twenty-one to be built in Alta California. Some fifty years later, in 1821, Mexico won its independence from Spain and secularized the

---

[18] Richard F. Pourade, The Explorers, The History of San Diego, Vol. 1., San Diego, CA: Union-Tribune Publishing Co., 1960.

[19] Syd Love, San Diego: Portrait of a Spectacular City, San Diego, CA: San Diego Magazine Publishing Co., 1969, p. 9.

mission system.[20] The Mexican government retained formal control of Alta California until 1848. During this period, officials handed out large land grants in exchange for political support. Vast ranchos were created and distributed to influential patricians. Much of present day San Diego County was parceled out in this way.[21] Effective Mexican control of the region and the San Diego settlement ended in 1846. The United States declared war on Mexico in May. By the end of July, U.S. marines had arrived in San Diego by sea and raised an American flag over the town's central plaza. The treaty ending the war ceded Alta California to the U.S. In February of 1850, California became a state of the union, and San Diego County was established. It then included, in addition to its present area, sweeping desert spaces that later became Imperial County, and large tracts now belonging to San Bernadino and Riverside counties. A month later, the city of San Diego was incorporated. The city's first mayor was Joshua Bean, brother of the famous West Texas hanging judge, Roy Bean.

San Diego's first decades as a U.S. city were eventful. The town prospered and grew rapidly.[22] In the 1850s, the town's first daily newspaper, the San Diego Herald, was published; a shipyard opened; a lighthouse was erected high above the

---

[20] Richard F. Pourade, The Time of the Bells, The History of San Diego, Vol. 2., San Diego, CA: Union-Tribune Publishing Co., 1961; and The Silver Dons, The History of San Diego, Vol. 3., San Diego, CA: Union-Tribune Publishing Co., 1963.

[21] Robert W. Brackett, The History of San Diego Ranchos: The Spanish, Mexican, and American Occupation of San Diego County and The Story of the Ownership of Land Grants Therein, 5th ed., San Diego, CA: Union Title Insurance Co., 1960; Harry C. Hopkins, History of San Diego and Its Pueblo Lands and Water, San Diego, CA: City Print Co., 1929; Richard F. Pourade, The Silver Dons, The History of San Diego, Vol. 3., San Diego, CA: Union-Tribune Publishing Co., 1963.

[22] See Richard F. Pourade, The Glory Years, The History of San Diego, Vol. 4., San Diego, CA: Union-Tribune Publishing Co., 1964; and Gold in the Sun, The History of San Diego, Vol. 5., San Diego, CA: Union-Tribune Publishing Co., 1965.

entrance to the harbor on Point Loma; and the first overland stage and mail route from the east was established. By 1860, the population had grown to more than 600, and the influx of newcomers continued to increase. In April 1867, fifty-four year-old real estate speculator Alonzo Horton arrived from San Francisco, having heard about San Diego in a lecture on California ports. He came with a dream of building a new frontier city.[23] For $265, Horton purchased nearly a thousand acres on the waterfront, several miles to the south of Mission Valley and the Presidio Hill settlement. Of his first view of the place, Horton later remarked: "I thought San Diego must be heaven on earth, if it all was as fine as that. It seemed the best spot for building a city I ever saw."[24] He plotted a grid of rectangular blocks and streets, and returned to San Francisco to open a land sale office.[25] From then on, urban development in San Diego centered on Horton's 'New Town.' Today, the city's downtown area and its high-rise office buildings stand on the ground that Horton first bought and sold. The Presidio Hill site has been known, since Horton's real estate operation got underway, as 'Old Town.'

As it grew, 'New Town' rapidly took on the look and character of a modern city. In the 1880s, telephone service and street lights were installed. A public library was opened, and a public streetcar transit system began to operate. The first railroad line to reach San Diego, the California Southern, running through Barstow, arrived in

---

[23] Elizabeth C. MacPhail, The Story of New San Diego and of Its Founder Alonzo E. Horton, San Diego, CA: Pioneer Printers, 1969.

[24] Richard F. Pourade, The City of the Dream, The History of San Diego, Vol. 7, San Diego, CA: Union-Tribune Publishing Co., 1977; p. 6.

1885, and the landmark Hotel del Coronado, a huge, red-roofed wooden structure perched on the beach, opened its doors in 1888. At its height, during this decade of prosperity, the city's population reached 40,000.[26] The real estate boom soon ended abruptly, however. The 1890s were a time of deep economic recession in San Diego, and the number of residents dropped precipitously. Not until 1910 would the city's population again reach 40,000. By that year, Los Angeles, located one hundred miles to the north, had already become a world class metropolis, a center of national and international finance, trade, and transportation with more than 320,000 residents. San Diego remained a relative backwater. The transformation of San Diego into a major U.S. city was a 20th century phenomenon. With more than 1.2 million people today residing within the city proper, San Diego has become a substantial urban hub in its own right. Its growth to this size was spurred initially by the arrival of a significant military presence in the County. San Diego geographer Phillip R. Pryde calls the years between 1908 and 1945 San Diego's "air and sea period,"[27] a time in which the city's economy became heavily dependent on war production.

Throughout its early history, urban development in San Diego was supported by growth in a highly diversified economy. San Diegans engaged in agriculture, livestock production, fishing, ship-building, and a wide variety of light industries. And, when advances in transportation around the turn of the century linked San Diego

---

[25] Hardigan Clower, "City Planning in San Diego," San Diego, CA: Works Progress Administration, 1938.

[26] Larry Booth, Roger Olmsted, and Richard F. Pourade, Portrait of a Boom Town: San Diego in the 1800's, San Diego, CA: San Diego Historical Society, 1977.

more conveniently to the rest of California and the country, the city became a popular destination for vacationers. The tourist trade became an important component of its economic base. But it was, above all, the arrival of the armed forces and the aviation industry in San Diego that provided the impetus for the massive growth that the city eventually experienced, and for the greater incorporation of San Diego into activities comprising the larger national scene. Naturally, the development of San Diego as a military town and the development of San Diego as an aviation town were closely linked.

The first major military installation in the city, a U.S. Army post called Fort Rosecrans (after a prominent businessman and U.S. Congressman from Southern California), was put in place in 1899, when, after the Spanish American War, the U.S. began to give consideration to strategic weaknesses on its southern flanks. The Navy paid a visit to San Diego in 1908, when the 'Great White Fleet,' comprised of sixteen battleships and seven other large vessels with 16,000 sailors aboard, chugged into port. The fleet had put San Diego on the itinerary of its world tour in order to give the top Navy brass a first close-up look at the harbor. In 1911, aviator Glenn Curtiss opened the world's first bona fide flying school, on Coronado's North Island. Army and Navy officers were among the first students, and the Army established an 'aviation camp' on the island. It was American participation in World War I, however, that really brought the armed forces to San Diego en masse. In 1917, as part of the huge military build-up undertaken prior to the American intervention, a new army base, this one much larger

---

[27] Philip R. Pryde, ed. San Diego: An Introduction to the Region, 3rd ed., Dubuque, IA: Kendall/Hunt, 1992; p. 8.

than Fort Rosecrans, was established several miles north of the city.[28] It was called Camp Kearney, after the Mexican War general. That same year, the airfield on Coronado's North Island was purchased by the government and turned into a joint Army and Navy air station, and several military hospitals were constructed in town. Then, in 1919, largely due to its proximity to the newly opened Panama Canal, San Diego Bay was chosen as the new home of the U.S. Pacific Fleet. The Navy constructed docks in various locations around the harbor and began building the massive shipworks that today stretch for miles along the South Bay. After the war, in 1923, a Marine Corps recruiting depot and a Naval Training Center were also opened in the city. San Diego had become heavily fortified and soon became known as a 'Navy town.' On the city's avenues, strolling sailors in uniform became a familiar sight, and the place would never be the same.

San Diego was also becoming known during this time as an 'aviation town.' The superb weather and flying conditions around the city have always attracted pilots, and San Diego has witnessed many aviation 'firsts.' John Montgomery, who later became a professor of physics and aerodynamics at Santa Clara College, is now credited by many – including the Smithsonian Institution – with the first controlled flight of a 'heavier than air' winged glider, on the breezy, open spaces of Otay Mesa, south of the city, in 1883. In 1911, the same year that he opened the world's first flight school in San Diego, Glenn Curtiss accomplished another novel aviation feat.

---

[28] In 1952, the site became Naval Air Station Miramar, home of the Navy's famous 'Top Gun' flight school. The Naval station was closed in 1998, and the installation was returned to the Marines, who now use it as a helicopter base.

After attaching pontoons to one of his aircraft, he made the first successful flight of a seaplane, taking off and touching down again in San Diego Bay.

In 1925, T. Claude Ryan and a partner established Ryan Airlines, Inc., which offered the first regularly scheduled commercial flights in the country, between San Diego and Los Angeles. Ryan recruited a group of aeronautical engineers and technicians to remodel his small fleet of planes for passenger use. In early 1927, this group manufactured Charles Lindbergh's plane, the 'Spirit of St. Louis.' Lindbergh put the plane through a series of test flights in San Diego, at the North Island airstrip, and then lifted off for the East Coast on May 9. His historic flight across the Atlantic began on May 20 and ended near Paris the following evening. Soon after, Lindbergh made his way back to San Diego, and 60,000 city residents turned out to cheer his return. Later in the year, aviation-happy San Diegans approved a bond issue to support the construction of a new municipal airport. Part of the bay near the downtown area was dredged and filled, and the runway was dedicated in 1928. Dubbed Lindbergh Field, it remains the city's principal commercial airport. San Diego has always been a place for fliers, and, throughout most of the 20th century, the city remained perched on the cutting edge of things aeronautical.[29]

Aircraft manufacturing supplanted agriculture as the region's main industry in the 1930s. Ryan commenced a commercial airplane-building venture in 1927, the Ryan Aeronautical Corporation. In 1930, George Prudden started a small firm called

---

[29] Mary L. Scott, San Diego, Air Capital of the West, Virginia Beach, VA: Donning Co., 1991; Syd Love, San Diego: Portrait of a Spectacular City, San Diego, CA: San Diego Magazine Publishing Co., 1969; Richard F. Pourade, The City of the Dream, The History of San Diego, Vol. 7., San Diego, CA: Union-Tribune Publishing Co., 1967.

the Solar Aircraft Company, which was initially housed in the same building as Ryan's company. Solar began to specialize in aircraft exhaust manifolds, other structural engine components, and, later, jet afterburners. It was eventually renamed Solar Turbines. In 1935, Reuben H. Fleet relocated his military aircraft building company, Consolidated Aircraft Corporation, to San Diego from Buffalo, New York, in order to take advantage of the better, and almost ideal, conditions for testing the flying boats that the company manufactured. A vast assembly plant was built along the Pacific Coast Highway adjacent to Lindbergh Field. In 1940, Fred Rohr, one of Ryan's engineers who helped design the 'Spirit of St. Louis,' founded the Rohr Aircraft Corporation. Rohr's venture focused on the design and manufacture of airplane engines and engine control systems. Each of these companies became a major San Diego employer (and would remain so for decades). Events taking place in far-flung places around the globe would soon make them much bigger.

World War II brought another population boom and another wave of industrial growth to San Diego. By 1940, the number of permanent residents in the city had risen to 200,000. By the end of the decade, it would exceed 333,000. The presence of the military in the San Diego expanded rapidly in the months before the bombing of Pearl Harbor on December 7, 1941. Afterwards, when the colossal war machine of the U.S. was fully mobilized and put into high gear, armed forces personnel and government contracts swarmed into the city in sometimes overwhelming numbers. New Army camps were established on Kearney Mesa, and near La Jolla, on a site that today belongs to the University of California, San Diego. The Navy built new airstrips and radar installations at various locations around the County. The air station

on Coronado began training pilots for the Air Force, and graduated more than 30,000 fliers annually during the war years. In 1942, the old Mexican Rancho Santa Margarita y Flores, encompassing 126,000 acres at the north end of San Diego County, was acquired by the Navy and transformed into the Camp Pendleton Marine base. The shipyards and aircraft factories expanded their operations and proceeded to work at full capacity around the clock. Through the war years, more than 75,000 San Diegans showed up for work each day at the Ryan, Solar, Consolidated, and Rohr plants, rolling planes and parts off massive assembly lines. At Consolidated (which, in 1943, merged with Vultee Aircraft in Downey, California, and was renamed Convair) nearly 7,000 B-24 Liberator bombers were welded together during the war, along with more than 21,000 other aircraft of various types. To absorb the influx of workers drawn to San Diego by this immense manufacturing effort, the federal government hastily erected thousands of tract houses in a new suburb, Linda Vista. The construction of homes proceeded so rapidly that the provision of goods and services to the new neighborhoods could not keep pace. Residents complained that they had to travel ten miles to purchase a loaf of bread.[30]

When World War II ended in 1945, many of the workers who had come to fill defense industry jobs in San Diego and many of the military veterans who had been stationed at local bases elected to stay on or return to the city. San Diego County, in fact, experienced a decline in population immediately following the war, and did not make up the numbers again until the early 1950s, but the total remained well above

---

[30] Richard F. Pourade, The City of the Dream, History of San Diego, Vol. 7, San Diego, CA: Union-Tribune Publishing Co., 1977; p. 33.

pre-war levels. Despite the inevitable peacetime cutbacks in production and jobs, many had discovered the charms of life in San Diego and were unwilling to give them up. The manpower that would be required for further economic progress was in place. In addition, thanks to the reshaping of American life by planes, trains, and automobiles, the city was no longer a lonesome, off-the-beaten-track border town. It had become accessible to the rest of the country. And future expansions of the city's population and economy were made possible, as well, by several massive public works projects undertaken, during and after the war, to bring new and greater supplies of freshwater to the city. Water would be crucial for the urban and industrial growth that was soon to occur in San Diego.

WATER AND ROCKETS

In this chapter about 'causal factors' or necessary preconditions that ought to figure into historical explanations for the emergence of the San Diego biotechnology industry, the social and technical engineering that delivered the city's supply of freshwater is perhaps the most important and most fundamental. Without imported water, the city of San Diego in its present form would not have become a realized possibility and the local biotech industry would almost certainly not have a history to explain. Most of San Diego County is semi-arid chapparal; moisture is scare. In the late 19th and early 20th centuries, dozens of dams, reservoirs, and aqueducts were built in various locations around the county in order to collect runoff from the Laguna and Cuyamaca Mountains, where rainfall is relatively plentiful. These stored waters were utilized for agricultural and industrial activity in and around the city, and to support

the growing population.[31] The region's naturally occurring groundwater supplies are enough to sustain several hundred thousand people on a modern scale.[32] In the 1930s, this limit on urban development in the San Diego environment had begun finally to appear on the horizon. San Diego, like many other Southern California communities, recognized and began to confront a looming crisis – future progress and increased wealth in the region would depend on the delivery of huge volumes of fresh water from distant sources.

In September of 1945, after more than a decade of planning and a long delay imposed by the war, construction began on a system that would siphon 55 million gallons of water per day from the Metropolitan Aqueduct, the channel through which Colorado River water is pumped toward Los Angeles, and carry it seventy-one miles to the south, through a series of tunnels and canals to the San Vicente Reservoir just outside the San Diego city limits. With engineering and manpower assistance from the U.S. Navy, the project was completed in just over two years; the first drops from the Colorado River arrived in San Diego in December 1947. Before the spigot was even turned, however, the future insufficiency of this supply was recognized, and, in San Diego, as in many other Southern California locales, public conversations commenced on additional sources and pipelines. Anticipating shortages sooner rather than later, state voters authorized the California Water Plan in 1960. The plan targeted

---

[31] Kyle Emily Ciani, "A Passion for Water: Hans H. Doe and the California Water Industry," Journal of San Diego History, 1993, 39, 4; Metropolitan Water District of Southern California, San Diego's Quest for Water, San Diego, CA: San Diego Citizen's Aqueduct Celebration Committee, 1947; "Water and San Diego County; A Study for the San Diego County Water Authority," Pheonix, AZ: Western Management Consultants, 1966.

the vast melting snow packs of the High Sierra as a new source. It called for water from the Feather River and surpluses from the Oroville Reservoir in the Gold Rush country of the Sierra foothills to be diverted hundreds of miles to the south in the largest water transfer project ever undertaken. Mountain snowfalls eventually arrived in San Diego in 1978. The problem of scarcity was solved.[33] With access to steady flows coming from the Colorado River and later the Sierra Nevada, the city has always had enough water to sustain growth and increased productivity.

After World War II, San Diego remained a 'Navy Town' and its economy continued to be dominated by industries that designed and manufactured products for military customers. Through the 1950s, the Cold War, the proliferation of nuclear weapons in the U.S. and the Soviet Union, the launch of Sputnik, and the ensuing international space race provided the city's aircraft manufacturers with ample opportunities to survive and resume growth. To a significant degree, San Diego's economic progress during this period was directly linked to technological developments, and, in particular, the expansion of national and international

---

[32] Philip R. Pryde, "Water Supply for the County," pp. 113-133 in San Diego: An Introduction to the Region, ed. Philip R. Pryde, Dubuque, IA: Kendall/Hunt, 1984.

[33] The solution was only temporary, of course. As long as economic expansion and population growth continue, more water will have to be delivered. Demand is nowhere subsiding while supplies are being depleted at rates that alarm environmentalists. For decades, Californians have been eyeing fresh sources. A 1966 study commissioned by San Diego County Water Authority reported that planners were entertaining the possibility of importing waters from as far away as the Columbia River, or even Alaska. See "Water and San Diego County," Phoenix, AZ: Western Management Consultants, 1966, p. 35. San Diego has secured enough water for the present, but not the future, and the political economy of water in the Western United States remains unsettled, as rapidly expanding cities, states, and industries compete for access to scare supplies. Biotech operations use a lot of water, and as they develop products and move into manufacturing, their requirements multiply. Access and costs will be significant concerns when, and if, San Diego companies begin evaluating possible sites for new manufacturing facilities. It is possible that new drugs will be designed in San Diego laboratories, but manufactured elsewhere. Civic leaders naturally hope to prevent desertions of this kind, but they may somehow have to guarantee water in order to do so.

transportation systems and the entry of the U.S. and the rest of the world into the space age. In 1953, Convair was purchased by General Dynamics, a huge aviation conglomerate then headquartered in New York City. After a disastrous attempt to compete with Boeing, Douglas, and Lockheed in the production of commercial jetliners, Convair refocused on the design and manufacture of jet fighters and high-altitude, long-range bombers deployed by the Strategic Air Command. The division also moved into aerospace production. In 1954, work commenced in San Diego on Atlas rockets, the launch vehicles for intercontinental ballistic missiles and, later, NASA spacecraft. The Air Force ignited the first successful test booster in 1957. Atlas vehicles were replaced in the U.S. nuclear arsenal by Thiokol's Minuteman missiles in 1965, but the space program continued to use them. Atlas rockets powered Mercury and Apollo astronauts into orbit and beyond, along with hundreds of satellite payloads, and the Ranger, Mariner, Pioneer, and Surveyor space probes. The huge Convair facility next to Lindbergh Field and another massive plant on Kearney Mesa kept many thousands of San Diegans busy throughout the Cold War period fashioning these giant candles, and later, Tomahawk missiles and space shuttle fuselages. Ryan Aeronautics also continued to manufacture military aircraft through the 1950s and 1960s, while diversifying into aerospace electronics, producing – notably – radar systems for NASA spacecraft, including those used on Apollo lunar landing modules. During this period, many smaller aerospace firms set up operations in San Diego, as well.

Between 1940 and 1960, San Diego's population more than doubled, expanding to greater than half a million people. In the 1950s and 1960s, the first

pieces of San Diego County's now extensive freeway system were constructed, the city's downtown skyline, which today features numerous high-rise office buildings towering over the bay, began to take shape, and new suburbs appeared and began to sprawl, extending the boundaries of the city further and further to the north and the east. The success of the defense industry was largely responsible for these developments. In 1960, aircraft, missile, and aerospace electronics production accounted for 72% of the dollar value of San Diego County's gross industrial output.[34] Still, for all the wealth that it generated, the aviation and aerospace sector could not provide a foundation for stable economic progress in the region. Sensitive to fluctuations in federal defense spending and allocations, the fortunes of the defense industry in San Diego rose and fell with shifts in political winds across the continent in Washington D.C., and around the world. The city and its defense contractors enjoyed spurts of industrial expansion during the '50s and '60s, but also periods of recession. In the middle of a particularly deep contraction, a 1965 Time magazine cover story referred to San Diego as 'Bust Town.' In the late 1960s, and especially during economic downturns, business and government leaders in the city began to applaud and encourage efforts to diversify the regional economy. The emergence of new programs of electronics and energy research and development in the city, along with increases in agricultural output, tourism, retail trade, and service industries began to wean the city partially from its heavy dependence on federal defense contracts. By the end of the 1960s, partly due to cutbacks in defense manufacturing, and partly due

[34] Love, San Diego: Portrait of a Spectacular City, p. 201.

to growth in other economic sectors, aviation and aerospace production accounted for less than 50% of the County's industrial output.[35]

Still, despite these changes in San Diego's economic profile, the end of the Cold War signaled hard times for the city in the early and mid-1990s. When U.S. defense spending was slashed, a wave of mergers and acquisitions overtook the aerospace industry, production was curtailed, and plants were sold or shut down all across the country. In the midst of this upheaval, General Dynamics closed its Convair division, including the two massive assembly facilities that had long since become San Diego landmarks, and pulled out of the city entirely. Solar, Rohr, and Ryan (renamed Teledyne Ryan after a merger in 1969) kept their doors open, but were forced to scale back their operations considerably. Many other local aerospace firms laid off workers en masse, or simply went out of business. The shipyards of the South Bay also felt the crunch. These workforce reductions sent the local economy into a tailspin (along with the rest of California, because of similar dependencies elsewhere in the state). The end of the Cold War meant that the aerospace industry could no longer serve as the principal foundation of San Diego's economic livelihood, and without this backbone in place, the city slumped into a deep recession. Yet, San Diego was able to recover rapidly from the blow.

The local economy was given renewed life in the 1990s by many smaller, 'knowledge-based' high-tech companies developing novel telecommunications, computer software, and biotechnological products.[36] Firms in this category conduct

---

[35] Love, San Diego: Portrait of a Spectacular City, p. 201.

[36] Rick Dower, "San Diego's Technological Turnabout," San Diego Magazine, June 1996, pp. 50-55.

business according to different operating principles than traditional 'vertically-structured' corporate hierarchies that relied on brute manufacturing power and confined concentrations of resources to generate profits and growth. They are designed for a new and different business environment – and, in fact, collectively create this environment – the 'new economy' in which growth is based on decentralized innovation and horizontal flows of information across formal organizational boundaries. Success and failure for these firms are not dictated by conventional economies of scale, but rather by the human capital and the collective know-how that they possess or lack. In the mid-1990s, San Diego was fortunate to have these firms in residence, along with the scientists and engineers – the 'think workers' – who make them go (although local industrialists still complain about a chronic shortage of skilled technicians). A number of these companies that had gotten modest starts two decades earlier were reaching levels of maturity that enabled them to cover some of the losses that San Diego had experienced following the decline of the aerospace giants. The seeds for this economic resurgence had been sown many years before, in the 1950s and 1960s, during what Dan Berger, Peter Jensen, and Margaret C. Berg have called San Diego's "educational renaissance."[37]

THE SCIENTISTS ARRIVE

Through World War II, San Diego's only institution of higher of learning was San Diego State College, which had been founded in 1897 as San Diego Teacher's College. The region's sole institution of academic scientific research was the Scripps

[37] Dan Berger, Peter Jensen, and Margaret C. Berg, San Diego, Where Tomorrow Begins, Northridge, CA: Windsor Publications, 1987; ch. 4.

Institution of Oceanography, established in La Jolla, in 1912. In the post-war era, however, San Diego was transformed into a world-class center of higher education, science, engineering, and medicine with remarkable alacrity. This transformation can be attributed, in part, to the optimistic faith in science and technology that spread across the U.S. in the 1950s. American science and technology had put an end to World War II in a spectacular manner, and the country readily embraced the vision of the postwar world promoted by Vannevar Bush, an influential advisor to U.S. Presidents, and director of the wartime Office of Scientific Research and Development . In 1945, Bush depicted the United States as a nation poised to explore an 'endless frontier' of economic prosperity and world dominance, a frontier on which scientists and technologists would be the trailblazers.[38] Commitment to this vision was contagious. In the 1950s, America's leaders at all levels were persuaded that economic progress and national security in the future would depend on advances in science and technology, and they were convinced that public investments in 'pure' science could be readily translated into practical benefits. America was ready to 'go nuclear,' and willing to throw money at the sciences in order to do so.[39]

A good deal of this money eventually found its way to San Diego. During the early years of the Cold War, federal policies authorizing expanded government support of basic scientific research convinced California legislators, political

---

[38] Vannevar Bush, Science: The Endless Frontier: A Report to the President on a Program for Postwar Scientific Research, Washington, D.C.: National Science Foundation, 1960 [1945].

[39] For a social history of the policy processes and debates that preceded definite funding commitments to the sciences at this historical juncture, see Daniel Lee Kleinman, Politics on the Endless Frontier: Postwar Research Policy in the United States, Durham, NC: Duke University Press, 1995. For case

administrators, educators, and businesspersons that real opportunities existed for enlarging the state's institutions of science and higher learning. San Diego's civic elite had long argued that the city deserved to be the site of a new UC campus, but these pleas had previously fallen on mostly deaf ears. After the war, however, the city's size, and the head start that it enjoyed in the development of space age technologies, thanks to its military installations and aviation and aerospace industries, made such arguments more persuasive and difficult to ignore. Advocates of the idea in San Diego, eager to secure the economic and cultural benefits that they anticipated a new university and center of academic scientific research would bring to the city, pressed the state and the UC system for action throughout the 1950s.[40] They were eventually rewarded for their efforts when a graduate school of science and engineering opened its doors in 1960, along the coast in La Jolla, on land donated by the city. Undergraduates first arrived for instruction in 1964.

---

studies, see Stuart Leslie, The Cold War and American Science: The Military-Industrial Complex at MIT and Stanford, New York: Columbia University Press, 1993.

[40] Influential support for the new school was lent, for example, by John Jay Hopkins, president of General Dynamics, which, in 1953, had acquired Convair, San Diego's largest employer. Hopkins envisioned San Diego as the site of a vital and progressive scientific-industrial-military complex. He promised to locate a nuclear energy research facility in San Diego if the city and the University of California would commit itself to generating an "appropriate academic atmosphere" to support it. In 1955, apparently satisfied that a new university was in the works, Hopkins opened General Atomics, a division of General Dynamics, on Torrey Pines Mesa in La Jolla. Hopkins also pledged that his corporation would donate $1 million to establish a center for research in physics on the new campus, if the school was located adjacent to the General Atomics complex. Five years later, it was. See Nancy Scott Anderson, An Improbable Venture: A History of the University of California, San Diego, La Jolla, CA: UCSD Press, 1993; p. 56. Gulf Oil purchased General Atomics in 1967. Today, the company is privately held. It still operates on Torrey Pines Mesa – the address now reads John Jay Hopkins Drive – pursuing a diversified research agenda, including work on lasers and cryotechnologies. Rental spaces in the monstrous, circular GA facility have housed numerous local high-tech and biotech ventures in their start-up phases.

One of the principal architects of the new university's charter was Roger Revelle, a marine geologist and scientific statesman of imposing stature – both physical and professional – who had been named director of the Scripps Institution of Oceanography in 1951. Initially, Revelle sought only to improve and expand graduate training and research at SIO, but he began eventually to lobby for the construction of a general university in San Diego as a new addition to the state-wide system. In 1955, the UC Regents ordered Revelle to compile a feasibility report on such an undertaking, and, in 1958, they approved a plan that bore the stamp of Revelle's politicking. Revelle imagined a "Cal Tech of the UC system," an institution dedicated mainly to the advancement of the physical sciences.[41] When the La Jolla campus was inaugurated in 1960, Revelle was named its chief administrative officer and the Dean of the School of Science and Engineering. The character of the university in its early years was shaped by Revelle's leadership and his insistence on recruiting to the new faculty only stellar scientists, only the most productive and well-respected contributors to their fields. Sunshine, intellectual ferment, and full professorships were dangled as bait, and many bit. From its inception, UC-San Diego was a premier institution of scientific research. Its founding was a key event in the transformation of San Diego into the mecca of science and high-technology that it has since become.

UCSD's academic departments and laboratories have continued to maintain their reputations for excellence. In 1994, the National Research Council ranked UCSD programs in oceanography, neuroscience, biomedical engineering, physiology,

---

[41] Nancy Scott Anderson, An Improbable Venture: A History of the University of California, San Diego, La Jolla, CA: UCSD Press, 1993; p. 38.

pharmacology, genetics, geosciences, cell biology, anthropology, political science, biochemistry, molecular biology, psychology, mechanical engineering, and aerospace engineering among the top ten in the country. The NRC rated the quality of the faculty in UCSD graduate programs overall as tenth best.[42] A recent analysis of scientific output at major U.S. universities found UCSD researchers to be the most productive in the country.[43] In 1994, the school ranked fifth in the nation in terms of attracting federal expenditures for scientific research, following Johns Hopkins, the University of Washington, MIT, and Stanford, and was first among public institutions. UCSD received $266.2 million. This figure was by far the highest in the UC system (UCSF received $213.3 million, UCLA was granted $190.2 million, and UC-Berkeley garnered $152.5 million). In 1996, public and private agencies together awarded UCSD researchers and programs a total of $325 million in contracts and grants.

By all reckonings, the university has lived up to its promise, not only as place where knowledge is advanced and culture is transmitted, but also as an engine of economic growth. In 1995, the school calculated that its operations the previous year had attracted $730 million to the San Diego region annually, that the total economic impact of the university on the local economy exceeded $1 billion, that its activities translated into 59,000 jobs locally and another 58,000 elsewhere, and that for every dollar invested by California in the San Diego campus, the school generated four more

---

[42] University of California, "Economic Impact," La Jolla, CA: University of California, San Diego, 1995.

[43] Hugh Davis Graham and Nancy Diamond, The Rise of American Research Universities: Elites and Challenges in the Post War Era, Baltimore, MD: Johns Hopkins University Press, 1997.

for the city, state, and nation.[44] These figures do not include the downstream impact of emerging technologies transferred from the university to private industry, a process that the university administration has worked to facilitate through the establishment of a number of different liaison offices and programs.[45] In 1997, the university estimated that at least 119 locally operated telecommunications, software, and biotech companies, with annual revenues exceeding $1.8 billion, were based on technologies developed at the school and its special centers, or founded by UCSD faculty, alumni, staff, and students. These numbers continue to increase; more UCSD-related start-ups follow on every year.[46]

The university has remained focused on the mission intended by the San Diego industrialists and politicians who championed its formation in the 1950s: the provision of practical technological and economic benefits to the city, the state, and the nation at large. Much of the scientific work performed at UCSD is conducted with definite utilitarian ends in mind. In addition to its many top-flight departments and laboratories of basic scientific inquiry, the campus houses numerous centers and institutes that concentrate on practical applications of research in areas such as supercomputing, wireless communications, materials sciences, structural engineering, optoelectronics, magnetic recording, nuclear fusion, energy conservation and pollution control, molecular genetics, biotechnology, biomedical engineering, biomedicine, and

---

[44] University of California, "Economic Impact," 1995.

[45] See University of California, San Diego, University Communications Office, "Partners in Business: A Guide to the Resources UCSD Provides for Business," La Jolla, CA: University of California, San Diego, 1997.

[46] University of California, San Diego, "Economic Impact Report," 1996; p. 5.

cancer research. These centers partner with industrial concerns and government agencies in a wide variety of arrangements, from contract research to, lately, joint commercial ventures, and their research agendas are often dictated by external interests.[47]

The original emphasis on the San Diego campus was the physical sciences, but top-flight bioresearchers were soon recruited to set up shop in La Jolla, as well.[48] Federal largesse conferred first on the physical sciences in the 1950s was soon extended to the biological and biomedical sciences, in addition, creating new opportunities for the expansion of training and research in these fields at institutions of higher education around the country. Almost immediately, UCSD began bringing in prominent life scientists to tap these resources and proceed with their investigations in laboratories and offices with ocean views. Renowned geneticist David Bonner came from Yale to put together the Department of Biology and to lead raiding parties around the country and the world to capture luminous colleagues. Bonner's efforts collected many trophies. The on-campus presence of these stars contributed significantly to the eventual formation of the biotechnology industry in the city. UCSD's life scientists soon came to constitute what Revelle had considered crucial for the development of a vibrant intellectual community and a world-class university – a 'critical mass' of bodies, minds, and know-how that could reproduce itself and generate and sustain its own independent scientific momentum. This 'critical mass'

---

[47] University of California, San Diego, University Communications Office, "Partners in Business."

[48] Nancy Scott Anderson tells of academic feuding in UCSD's early days that had to do mainly with "biology's challenge to the campus dominance of physics." See Anderson, An Improbable Venture, pp. 139-141.

was not long limited to the new UC campus, however. Around the same time that prominent biologists and biochemists began arriving at UCSD, other chains of events were unfolding locally in ways that would deliver more stellar bioresearchers to the city. Eventually, for a brief time in the late 1970s and early 1980s, most of them would congregate on a small patch of ground in La Jolla, occupying labs in three institutions located within shouting distance of the intersection of North Torrey Pines Road and Genesee Avenue.

THE OTHER PLACES AROUND UCSD

In addition to UCSD, North Torrey Pines Road is today the address of the Scripps Research Institute, the world's largest not-for-profit biomedical research facility. The institute was established in 1955. The Scripps story begins around the turn of the 19th century, when Ellen Browning Scripps, along with her brother, Edward W. Scripps, decided to retire to a San Diego County ranch. From the ranch, the pair directed a newspaper empire, consisting of nineteen periodicals in various cities around the country, that they had begun building together in the 1870s. Ellen became known in the area as a generous philanthropist (Edward W. did not). She provided most of the funds that zoologist William E. Ritter used to transform a tiny marine biology station in La Jolla into a leading center of ocean science that was administered, after 1912, by the University of California – the Scripps Institute of Oceanography. She also financed the construction of Scripps Memorial Hospital in La Jolla in 1924. Today a large chain of medical centers, Scripps Memorial has facilities all around the county. That same year, Scripps donated money for the establishment

of Scripps Metabolic Clinic, an entity independent of the hospital.[49] In 1955, the clinic decided to expand its research activities, and reorganized itself as the Scripps Clinic and Research Foundation. In 1977, the foundation was moved to Torrey Pines Mesa, just north of UCSD, on oceanfront property donated by Dow Chemical. Dow had planned to build a napalm manufacturing facility on the site, but gave up on the idea as the war in Vietnam began to wind down. When the clinic and the research institute became affiliated with Scripps Memorial Hospitals in 1991, their administrations were partitioned. Each became a separate corporation under the umbrella of a larger parent, the Scripps Institutions of Medicine and Science

In 1961, Scripps lured leading immunologist Frank Dixon and four colleagues away from the University of Pittsburgh, and, with this acquisition, entered the arena of big-time biomedical research.[50] With its reputation boosted by the presence of Dixon's team, Scripps was able to begin attracting many other high-profile bioscientists. Today, the quality of the faculty and the research conducted at the institute is internationally recognized. The size of the operation is impressive. Scripps is home to roughly 300 faculty members, 800 postdoctoral fellows, 140 graduate students, 1,500 technical and administrative support personnel, and one million square feet of laboratory space. Work at the institute is divided among eight different departments: cell biology, chemistry, immunology, molecular biology, molecular and

---

[49] San Diego Historical Society, "San Diego Biographies: Ellen Browning Scripps (1836-1932)," http://www.sandiegohistory.org/bio/scripps/ebscripps.html.

[50] See Scripps Clinic and Research Foundation, Office of Development, Scripps Clinic and Research Foundation: A Brief History, La Jolla, CA: Scripps Clinic and Research Foundation, 1984; and Research Institute of Scripps Clinic, Research Institute of Scripps Clinic: A Twenty-Five Year History, La Jolla, CA: Research Insititute of Scripps Clinic, 1986.

experimental medicine, vascular biology, neurobiology, and neuropharmacology. Within these units, Scripps scientists pursue both basic inquiries into fundamental biological and biochemical processes and research on potential therapies for a host of serious infectious, genetic, and autoimmune diseases, including AIDS, allergies, Alzheimer's disease, cancer, diabetes, hepatitis, and multiple sclerosis.

Under the leadership of current president Richard A. Lerner, Scripps has aggressively pursued ever closer working relationships with pharmaceutical companies in order to fund its research (in part, because the institute is not affiliated with a university, and lacks the infrastructural support that such institutions provide to the sciences).[51] These arrangements have broken new ground in the organization of biomedical science, and they have sometimes been controversial.[52] The impacts that academic-industry alliances and the commercialization of scientific knowledge will have on the character of future research remain uncertain. Lerner, a productive immunologist with a long record of achievement, has, in the course of conducting his own research, become personally embroiled in disputes about norms of scientific conduct, communication, patents, and conflicts of interest.[53] In addition to generating new knowledge, scientists and administrators at places like Scripps are transforming the conditions under which scientific inquiries are conducted, and they have received plenty of criticism for it. Still, the institute is proud of its history and optimistic about

---

[51] See Josh Lerner, "The Scripps Research Institute," Harvard Business School Case 295-068, Cambridge, MA: Harvard Business School, 1994.

[52] See Christopher Anderson, "Scripps Backs Down on Controversial Sandoz Deal," Science, 1993, 260: 1872-1873; Anderson, Christopher, "Proprietary Rights – Scripps-Sandoz Deal Comes Under Fire," 1993, 259: 889; Ann Gibbons, "Scripps Signs a Deal With Sandoz," Science, 1992, 258: 1570.

what is yet to come. Its promotional materials call Scripps "a name that will likely be associated with some of the greatest biomedical advances of the decades ahead."[54] Perhaps, but scientists at Scripps have already done much to advance the technical capacities of biomedicine; technologies developed at the institute have already served as the basis for dozens of new biotechnology companies in San Diego and elsewhere.

A third center of cutting-edge bioscience, and another draw for leading experts in biomedical fields, appeared on North Torrey Pines Road in 1963, when Jonas Salk, inventor of the world's first polio vaccine, came to town and established another private, not-for-profit research organization, the Salk Institute for Biological Studies. Taking advantage of his notoriety and the acclaim that he had received following the introduction of his vaccine, Salk began to investigate possibilities for leaving the University of Pittsburgh Medical School, where his work on polio had been conducted, to set up his own house of research in a more enticing setting. In 1960, having secured a $20 million grant from the National Science Foundation, and additional support from the March of Dimes, Salk accepted an invitation from the city of San Diego and the new academic community at UCSD to visit and discuss the ways in which a La Jolla location and proximity to the growing university might be beneficial for his project. When he arrived, Mayor Charles Dail, a childhood polio victim, offered, with the permission of the City Council, to donate land and suggested a number of municipal properties as possible sites. Salk was taken by La Jolla and selected seventy prime acres overlooking the Pacific, lands that had previously been

---

[53] Nicholas Wade, "La Jolla Biologists Troubled By the Midas Factor," Science, 1981, 213: 623-628.

[54] "TSRI – History," http://www.scripps.edu/intro/history.html.

promised to UCSD. The gift became a source of conflict. Some university administrators did not wish to surrender rights to the property. Roger Revelle and Salk sniped at each other publicly, and privately engaged in a series of bitter shouting matches, but still eager to have Salk relocate in La Jolla, university officials eventually acquiesced.[55]

Research at the Salk got underway in 1963, and, in 1967, a new laboratory facility designed by architect Louis Kahn was dedicated. The building has been hailed widely as a masterpiece of modern architecture. Its stark concrete perimeter conceals a tranquil and harmonious light-splashed inner courtyard that frames stunning views of the blue sky above and the blue Pacific below. Today, most Salk researchers (seventy principal faculty members and many more staff scientists and graduate students work on site) conduct basic inquiries in molecular biology and genetics. Numerous ongoing investigations are focused directly on disease mechanisms and processes that work at the molecular level. The institute has also become known as a leading center for the study of the brain. The Salk presently administers nine different research programs in neurobiology and cognitive science. It hosted Nobel laureate Francis Crick, co-discoverer, with James D. Watson, of the double-helical structure of the DNA molecule, until his recent death in San Diego. Crick spent his later years theorizing about the material substrates of consciousness.[56] Salk scientists regularly collaborate with colleagues at UCSD and Scripps, and, although Jonas Salk himself declined to

---

[55] Nancy Scott Anderson, An Improbable Venture, pp. 61-62.

[56] See Francis Crick, The Astonishing Hypothesis: The Scientific Search for the Soul, New York: Scribner's, 1994.

patent the polio vaccine that he invented, his institute actively pursues opportunities to license intellectual properties and transfer technologies to industry for further development. Salk technologies have formed the basis of some of San Diego's largest biotech companies.

Many other biological and biomedical research institutes have been established in San Diego since the 1970s, and they have contributed to the vitality of the life science community in the city, but the formation of one other organization was especially important in the development of San Diego's 'critical mass' of bioscientific expertise and the growth of the local biotechnology industry.[57] Plans for opening a medical school affiliated with UCSD had been on the university's agenda from the time the school was founded. Due to prolonged administrative wrangling within the UC system, and extended budget negotiations between the university, the UC Regents, and the statehouse in Sacramento, the first facilities and the first class of medical students did not materialize until 1968.[58] At issue was the kind of professional training that would take place at the new school. Faculty and administrators in San Diego envisioned an institution that would, of course, carry out the traditional functions of a medical school – teaching, patient care, and research – but with a

---

[57] The growth of San Diego State University has also been an important part of the city's 'educational renaissance' and its emergence as a contemporary center of science and high-tech innovation. Formerly San Diego State College, the school achieved university status in 1971, and became part the massive California State University system. In 1994, it was designated a doctoral institution, and began granting Ph.D.s in conjunction with other schools. Today, more than 25,000 undergraduates enroll at SDSU each semester, and the university ranks number one among Cal State campuses in terms of attracting public and private research grants and contracts, nearly $100 million annually in recent years. Numerous smaller schools and community colleges are located in the city, as well, along with the University of San Diego, a Roman Catholic institution with 7,000 undergraduate and professional students.

[58] Anderson, An Improbable Venture, ch. 7.

decided emphasis on the latter, and more specifically, with a decided emphasis on basic rather than clinical research. In keeping with the strong commitment of the campus to academic science, the plan was to integrate the life science faculties of the general university into the medical school curriculum and to train medical students in laboratories conducting basic biomedical investigations. UCSD intended to produce a new generation of physician-scholars.

Lawmakers and budgeteers in Sacramento, and the California Medical Association, too, were not enthusiastic about manufacturing more scientists; they were more interested in preparing the state to cover a predicted shortfall of practicing doctors at a reasonable cost. UC system officials were naturally sensitive to these practical concerns. A series of compromises resulted, and the Regents eventually endorsed a mission of "broad-gauged and high quality education of physicians for service."[59] When the UCSD School of Medicine finally opened its doors for the first time, a roster of famous clinicians and practitioners had been recruited, and had assumed positions of power within the institution. This group, despite the concerted opposition of the academics, was able to influence considerably the direction of the place. The school was established with a built-in identity crisis, and never became the temple of pure medical science that many of the academicians on campus taking part in the project had hoped it would.

Still, the research component of the program, including a commitment to basic inquiry, remained the school's primary focus and selling point, and it continues to be

---

[59] Anderson, An Improbable Venture, p. 157.

an identifying characteristic of the institution. The UCSD School of Medicine has developed a national reputation for excellence in both basic and clinical biomedical science. It is ranked consistently among the top ten in the country. Medical school scientists and clinicians collaborate with numerous campus centers engaged in 'basic' and 'applied' research on the mechanisms, treatment, and prevention of disease, including the UCSD Cancer Center, the Center for Molecular Genetics, and the Biomedical Engineering Institute. More than four hundred faculty members perform laboratory or clinical investigations that are supported more than $130 million annually in sponsored research funding. No medical school in the nation has more principal investigators conducting federally funded research.[60] Many of the most prominent and prolific bioscientists in San Diego are faculty members at the UCSD School of Medicine, and many of them have become active scientific entrepreneurs, transferring their work to industrial labs, through various means, when they have generated new knowledge or developed new techniques of practical medical use and apparent commercial value. Like San Diego's many other bioresearch organizations, the UCSD School of Medicine has encouraged this kind of activity, and has attempted to streamline the process.[61]

MOLECULAR BIOLOGY AND BIOLOGICAL IMMUNOLOGY

The fields of scientific inquiry that laypersons typically associate with biotechnology – because they have received the most attention from the press – are

---

[60] Anderson, An Improbable Venture, p. 1.

[61] See UCSD School of Medicine, "A Study of the Biotechnology Transfer Process," La Jolla, CA: UCSD School of Medicine, October 1987.

molecular biology and molecular genetics.[62] The business of biotechnology came into being in the 1970s on the heels of an important advance that signaled, to forward-looking observers, the feasibility of applying cutting edge research in these areas to commercial ends. In 1973, biochemist Herbert Boyer, working at the University of California, San Francisco, and geneticist Stanley Cohen, at the Stanford School of Medicine, together pioneered techniques for manipulating the expression of proteins in microbes. They inserted active bits of foreign DNA (genes from the African clawed toad, Xenopus laevis) into E. coli bacteria, and recombinant DNA, or 'gene splicing,' technology was born. The scientific groundwork for this breakthrough began much earlier with the development of new tools and new forms of biological thinking in the late 1930s. The ascendance and articulation of the molecular 'paradigm' in biology during the middle decades of the 20th century laid the theoretical and technical foundations on which later biotechnological innovations such as 'gene-splicing' would be built.[63] In fact, some recent historians of science adopting 'internalist' approaches (those that tend to privilege conceptual developments in scientific fields as explanations for the production of new scientific facts and theories) have treated the

---

[62] The field of biotechnology today encompasses work conducted in many different scientific disciplines. The diversity of R&D projects undertaken by biotech firms (and, often, their academic collaborators) is impressive. Later chapters of this work detail numerous approaches to drug discovery and development explored by biotechnologists in private laboratories in San Diego.

[63] On the history of molecular biology, see Garland Allen, Life Science in the Twentieth Century, New York: John Wiley & Sons, 1975, ch. 7; Soraya de Chadarevian, Design for Life: Molecular Biology after World War II, Cambridge: Cambridge University Press, 2002; S.F. Gilbert, "Intellectual Traditions in the Life Sciences: Molecular Biology and Biochemistry," Perspectives in Biology and Medicine, 26: 151-162; Horace Freeland Judson, The Eighth Day of Creation, New York: Simon & Schuster, 1979; Michael Morange, A History of Molecular Biology, trans. Matthew Cobb, Cambridge, MA: Harvard University Press, 1998; R.C. Olby, The Path to the Double Helix, New York: Macmillan, 1974; John W. Servos, Physical Chemistry from Otswald to Pauling: The Making of a Science in America, Princeton, NJ: Princeton University Press, 1990; and Edward Yoxen, "Giving Life a New Meaning: The Rise of the Molecular Biology Establishment," Sociology of the Sciences 6: 123-143.

emergence of the biotechnology industry mostly as an addendum to the rise of molecular biology.[64]

The development of molecular biology was profoundly influenced by a migration of theoretical physicists to the study of biological topics and questions in the 1930s.[65] This group believed that investigating the physical configurations and properties – the 'stereochemistry' – of biological substances and organisms would lead them to 'the secret of life.'[66] They supplemented the serological and microbiological experimental methods that had previously dominated biochemistry and genetics with new tools including electron microscopy and x-ray crystallography, techniques used to map the structures of molecules in three dimensions, and fractionation procedures like ultracentrifugation, chromatography, and electrophoresis, which are used to separate and purify components of biological substances according to molecular weight or by electrical charge.[67] The ferment of research into the molecular basis of life using these

---

[64] See, for example, Horace Freeland Judson, The Eighth Day of Creation: Makers of the Revolution in Biology, New York: Simon & Schuster, 1979; Michael Morange, A History of Molecular Biology, trans. Matthew Cobb, Cambridge, MA: Harvard University Press, 1998. Cf. Robert Bud, The Uses of Life: A History of Biotechnology, Cambridge University Press, 1993.

[65] For a social history of the phenomenon, see Evelyn Fox Keller, "Physics and the Emergence of Molecular Biology: A History of Cognitive and Political Synergy," Journal of the History of Biology, 1990, 23: 389-409.

[66] An influential statement of this view was offered by Erwin Schrödinger in What is Life? The Physical Aspect of the Living Cell & Mind and Matter, Cambridge: Cambridge University Press, 1967 [1944].

[67] For historians' takes on the significance of new technologies in the development of molecular biology, see Lily E. Kay, "Laboratory Technology and Biological Knowledge: The Tiselius Electrophoresis Apparatus, 1930-1945," History and Philosophy of the Life Sciences, 1988, 10: 51-72; and Nicolas Rasmussen, "Making a Machine Instrumental: RCA and the Wartime Origins of Biological Electron Microscopy in America, 1940-1945," Studies in History and Philosophy of Science, 1996, 27: 311-349. Kay notes that as research was organized increasingly around expensive new technologies, many areas of biological inquiry were transformed into 'Big Sciences.' For case studies framed by a similar theoretical agenda, see Adele E. Clarke and Joan H. Fujimura, eds., The Right Tools for the Job: At Work in the 20th Century Life Sciences, Princeton, NJ: Princeton University Press, 1992.

new tools came to fruition with James D. Watson and Francis Crick's discovery of the double-helical structure of the DNA molecule. Watson and Crick (originally a theoretical physicist), were, like many others at the time, led into their work by prior experiments indicating that simple DNA molecules, and not proteins, contained the basic genetic information that supervises the assembly of all other cellular materials, which then interact and move through the dazzlingly complex metabolic pathways that constitute life.[68] Watson reports, in his autobiographical account of the discovery process, that the pair arrived at their conclusions principally by combining Rosalind Franklin's structural X-ray diffraction data with basic knowledge of chemical bonds and the chemical composition of the molecule.[69]

In the concluding lines of their landmark paper, Watson and Crick famously wrote: "It has not escaped our notice that the specific pairing [of the molecule's constituent purine and pyrimidine bases] we have postulated immediately suggests a

---

[68] Microbiologist Oswald Avery is generally credited with producing the clinching evidence in experimental work conducted at the Rockefeller Institute in New York in the early 1940s, although his findings did not initially convince many colleagues. Biologists and geneticists were simply not prepared to accept that a molecule as simple and humble as DNA made up genes. Avery's proof came from an experiment on pneumococcus bacteria. Pneumococcus appears in two different forms – a virulent 'S' (smooth) strain and a non-infectious 'R' (rough) strain. Avery extracted and purified DNA from S pneumococci and added it to a colony of the R type. In the culture of inactive rough-coated bacteria there began to appear new generations of the virulent smooth strain. The experiment is simple, and the transformation of bacterial types had been observed before, but because biologists believed that proteins must be involved, no one had thought to experiment with purified DNA. Avery accidently stumbled across it when he developed a procedure for separating the inner contents of S pneumococcus cells from their outer coats. After disposing of the outer cell membranes, the remaining substance continued to produce the genetic transformation. Avery then conducted a series of systematic chemical analyses to isolate the active agent in the mix. The process of elimination revealed that it was, in fact, DNA. For an account of Avery's experiments and their reception, see Horace Freeland Judson, The Eighth Day of Creation: The Makers of the Biological Revolution, New York: Simon & Schuster, 1979; pp. 14-23.

[69] James D. Watson, The Double Helix: A Personal Account of the Discovery of the Structure of DNA, ed. Gunther S. Stent, New York: W.W. Norton & Co., 1980 [1968].

possible copying mechanism for the genetic material."[70] With the structure of DNA in hand, molecular biologists began to investigate the ways in which genes replicate and function. The new paradigm in biology enabled researchers to read the molecular language of the cell and to begin filling in the blanks of the 'central dogma' of molecular biology – the idea that genetic information is transmitted from the coded arrangement of nucleotide base pairs in the DNA molecule via RNA to sites of protein synthesis. Researchers began to detail the complex polymerase enzyme-driven processes of DNA synthesis and RNA transcription, to elucidate the roles of mRNA (messenger), tRNA (transfer), and rRNA (ribosomal) in 'translation,' i.e., the selection, ordering, and linking of the amino acids that constitute protein molecules, and to develop techniques for mapping genes on chromosomes and isolating and characterizing specific DNA sequences.[71] With the identification, in the late 1960s, of restriction and ligating enzymes that permit researchers to 'cut and paste' fragments of DNA, the scientific stage was set for the development of recombinant DNA (rDNA) techniques.

In 1972, in San Francisco, Boyer was investigating restriction enzymes that cleaved DNA molecules at specific intervals. At the same time, in Palo Alto, researchers at Stanley Cohen's Stanford lab were busy with their efforts to clone genes in E. coli. They were inserting into bacterial plasmids – small circular strands of DNA

---

[70] J.D. Watson and F.H.C. Crick, "A structure for deoxyribose nucleic acid, Nature, 1953, April 25: 737-738.

[71] The most complete historical account of these developments is Horace Freeland Judson's The Eighth Day of Creation: Makers of the Biological Revolution, expanded edition, Plainview, NY: Cold Spring Harbor Laboratory Press, 1996.

– foreign genetic material in order to confer on the microbes and their descendants in subsequent generations resistance to antibiotics. Learning about each other's projects at a conference in Hawaii, Boyer and Cohen realized that their methods and objectives could be complementary. They decided to team up. Working together, they found an enzyme that reliably snipped E. coli plasmids at a definite location, leaving 'sticky ends' on the broken strands. The sticky ends allowed the researchers to introduce foreign genes into the breach. When they managed to culture microorganisms that produced proteins ordinarily found in African clawed toads and not bacteria, the era of genetic engineering had begun, and the birth of the biotechnology industry followed on shortly after.

Stanford patented Boyer and Cohen's technique, and, for the bother, received $250 million in royalties over the years before the patent expired in 1997. The invention was commercialized on April 7, 1976, with the incorporation of Genentech, the world's first dedicated biotechnology company. Genentech was initially a collaboration between Boyer and Bay Area venture capitalist Robert Swanson. Although Cohen was enthusiastic about practical applications of recombinant DNA techniques, he was reluctant to capitalize on the breakthrough and declined to participate. Boyer and Swanson envisioned production at the company taking place in tiny biological factories that would generate proteins and other substances to be used as medicinal therapies and for a variety of other purposes. They recruited a group of young post-docs to push forward the firm's R&D operations, and to compete with leading academic researchers working simultaneously with rDNA, notably William

Rutter and Howard Goodman at UCSF and Walter Gilbert at Harvard, in a scientific race to clone a human gene.[72]

In 1977, Genentech scientists beat the academics to the finish line, and became the first to coax a gene into expressing a human protein, somatostatin, in a microorganism (but not without difficulties that almost sunk the company). Genentech had no intention of marketing somatostatin, a relatively simple brain hormone, comprised of only fourteen amino acids. The work was conducted to demonstrate the utility of recombinant DNA technology, and to attract investors. The following year, the Genentech scientists cloned the gene that expresses human insulin, a much more complex molecule. This was the real prize that the company was after, because the market for human insulin (dominated for years by Eli Lilly) is enormous. The next target was human growth hormone. The gene for HGH was synthesized in 1979. Genentech's pilot manufacturing facility was soon filled with vats of bacteria spitting out these substances in large quantities. In 1982, the company's human insulin became the first recombinant product approved by the FDA and the first to reach the shelves of pharmacies. (Dubbed 'humulin,' it was, and still is, distributed by Lilly, which had purchased manufacturing and selling rights in exchange for R&D support and downstream royalties). Molecular biology had gone to market.

While molecular biologists have played important roles in the development of biotechnologies in San Diego, the very first scientific entrepreneurs in the city were

---

[72] Stephen S. Hall, Invisible Frontiers: The Race to Synthesize a Human Gene, New York: Atlantic Monthly Press, 1987. See also "Recombinant DNA Research at UCSF and Commercial Application at Genentech" [interview with Herbert W. Boyer, Ph.D.], UCSF Oral History Program and the Program in the History of the Biological Sciences and Biotechnology, The Bancroft Library, University of California, Berkeley, 2001.

people involved in the fields of immunology, cell biology, and cancer research. The disciplinary history of immunology, and particularly trends within it that emerged in the 1950s and 1960s, had a direct bearing on the early formation of the San Diego's biotech industry in the 1970s.[73] The modern science of immunology shares its origins with bacteriology and serology, and early practitioners drew up research agendas that were influenced significantly by medical and public health concerns.[74] From the beginning, they were concerned with explaining the phenomenon of immunity – the mysterious and apparently healing 'commotion in the blood' that accompanies infectious illness.[75] The germ theory of disease promoted by Pasteur and Koch and the corollary notion of biological specificity provided researchers in the late 19th century with a conceptual framework for investigating it. The early immunologists experimented with soups – blood, serum, and microbial cultures – in order to identify disease-causing agents and to develop antidotes and prophylactic vaccines. However, while they discovered that immunity could be induced, successes in treatment and prevention were limited.

---

[73] For broad histories of the science of immunology, see Debra Jan Bibel, Milestones in Immunology: A Historical Exploration, Madison, WI: Science Tech Publishers, 1988; Pauline M. Mazumdar, ed., Immunology 1930-1980: Essays on the History of Immunology, Toronto: Wall & Thompson, 1989; Arthur M. Silverstein, "The History of Immunology," ch. 2 in Fundamental Immunology, 4th ed., ed. William E. Paul, M.D., Philadelphia, PA: Lippincott-Raven, 1999; and Arthur M. Silverstein, A History of Immunology, San Diego: Harcourt Brace Jovanovich, 1989.

[74] See Allan Chase, Magic Shots: A Human and Scientific Account of the Long and Continuing Struggle to Eradicate Infectious Diseases by Vaccination, New York : Morrow, 1982; Timothy Lenoir, "A Magic Bullet: Research for Profit and the Growth of Knowledge in Germany around 1900," Minerva, 1988, 26: 66-88; Dorothy Porter and Roy Porter, "The Politics of Prevention: Anti-Vaccinationism and Public Health in 19th-century England," Medical History,1988, 32: 231-252.

[75] Stephen S. Hall, A Commotion in the Blood: Life, Death, and the Immune System, New York: Holt, 1997.

Basic biological and chemical knowledge of the substances responsible for the immunologic properties of blood and serum remained impoverished during the discipline's formative years. Leon Chernyak and Alfred I. Tauber credit Ilya Metchnikoff with formulating the first modern immunological theory, in 1883.[76] Metchnikoff attributed immune activity to phagocytic white blood cells. In 1890, however, von Behring and Kitasato demonstrated that injections of serum purged of cells could confer passive immunity, and attention in the field was turned away from cellular activity to humoral factors. Immunologists began searching for invisible 'magic bullets,' as Paul Erlich dubbed them around the turn of the century – antitoxic substances that apparently circulated in the blood, contacting and rendering impotent harmful microbes and other pathogens. Erlich's influential 'side chain' theory was the first to conceptualize antitoxins, or antibodies, as they would soon come to be known. Erlich theorized that antitoxins were nutrient receptors on cell surfaces. He hypothesized that when an organism is exposed to foreign disease causing agents, these 'side chains' were released into the bloodstream to neutralize the pathogens (or antigens – i.e., antitoxin generating particles).[77] The bacteriological and serological

---

[76] Leon Chernyak and Alfred I. Tauber, "The Idea of Immunity: Metchnikoff's Metaphysics and Science," Journal of the History of Biology, 1990, 23: 187-249.

[77] Historians interested in demonstrating the 'embeddedness' of immunological knowledge in broader cultural processes have lately focused on the epistemological underpinnings of immunological theory, and on the rhetorical elements of immunological language, and, in particular, the use of military metaphors – invasion, defense, mobilization, and so on. Among the many works of this kind are Alberto Cambrosio, Daniel Jacobi, and Peter Keating, "Erlich's 'Beautiful Pictures' and the Controversial Beginnings of Immunological Imagery," Isis, 1993: 662-699; Eileen Crist and Alfred I. Tauber, "Debating Humoral Immunity and Epistemology: The Rivalry of Immunochemists Jules Bordet and Paul Erlich, Journal of the History of Biology, 1997, 30: 321-356; Fred Karush, "Metaphors in Immunology," pp. 73-80 in Immunology 1930-1980: Essays on the History of Immunology, ed. Pauline Mazumdar, Toronto: Wall & Thompson, 1989; Peter Keating and Alberto Cambrosio, "Helpers and Suppressors: On Fictional Characters in Immunology," Journal of the History of Biology, 1997, 30: 381-396; Ilana Löwy, The Immunological Construction of the Self, Dordrecht, Netherlands: Kluwer

methods of the day, however, did not permit immunologists to locate these invisible antibodies empirically or to explain precisely how they functioned. Only their effects could be observed. Around 1910, researchers in the field began to turn away from serology toward chemistry in order to identify and characterize antibodies and to account for their neutralizing activity.

The outstanding questions in the field became those that Erlich's theory left unanswered. Given the diversity of antigens that can elicit immune reactions, the specificity of antibodies, in particular, remained a puzzle. Many immunologists found it difficult to accept that bodies naturally produced a repertoire of pre-formed specific antitoxins so large as to prepare them for any occasion of infection or intrusion by a foreign substance. Template or instructional theories began to gain favor in the field.[78] These postulated that generic antibodies fold themselves around antigens, becoming specific in the process – antigens must 'teach' antibodies their specificity. Starting from this basic assumption, immunologists began to focus narrowly on the chemistry of antibody-antigen interactions. Questions about biological function took a back seat to questions about antibody structure and folding, and immunology became, for some

---

Academic, 1991; Pauline M. Mazumdar, "The Purpose of Immunity: Landsteiner's Interpretation of the Human Isoantibodies," Journal of the History of Biology, 1975, 8: 115-133; Anne Marie Moulin, "Text and Context in Biology: In Pursuit of the Chimera," Poetics Today, 1988, 9: 145-161; Thomas Söderqvist, "Darwinian Overtones: Niels K. Jerne and the Origin of the Selection Theory of Antibody Formation," Journal of the History of Biology, 1994, 27: 481-529; Alfred I. Tauber, The Immune Self: Theory of Metaphor? Cambridge: Cambridge University Press, 1994; Alfred I. Tauber and Leon Chernyak, Metchnikoff and the Origins of Immunology: From Metaphor to Theory, New York: Oxford University Press, 1991. For a conceptual alternative to warfare imagery, see Marc Lappé, The Tao of Immunology: A Revolutionary New Understanding of Our Body's Defenses, New York: Plenum Trade, 1997.

[78] Physical chemist Linus Pauling produced one of the last and most sophisticated of these theories. See L. Pauling, "A theory of the structure and process of formation of antibodies," Journal of the American Chemistry Society, 1940, 62: 2643-2657.

four decades, largely the study of immunochemistry. Historian Arthur M. Silverstein calls this period the 'Dark Ages' of immunology.[79] Many developments in the field during this time paralleled the new structural biology (although the molecular genetic foundations of immunity were left largely explored), antibodies were first identified and characterized as real substances, and much was learned about the 'stereochemical' features of humoral immunity. Silverstein notes, however, that when immunologists adopted the language of chemistry as their mother tongue, the discipline became increasingly insular, in both intellectual and social terms. Its contacts with larger communities of biological scientists diminished, and, consequently, the field became stuck with theories of immunity that most practitioners themselves felt were inadequate.

A major shift in the character of the field began in the 1950s, when some immunologists decided to take time off from the study of antibody chemistry to address the lingering problems of template theories of specificity. One established immunological fact with which these theories could not contend was the continuous production of specific antibodies after antigens had been cleared from the body. In 1955, Niels Jerne proposed a theory of antibody formation that hearkened backed to Erlich's, and resolved this difficulty by incorporating ideas about biological function.[80] He proposed that pre-formed specific antibodies bind with antigens, and that the resulting antigen-antibody complexes are consumed by phagocytic cells. The

---

[79] Arthur M. Silverstein, A History of Immunology, San Diego: Harcourt Brace Jovanovich, 1989; pp. 329-330.

[80] Thomas Söderqvist, "Darwinian Overtones: Niels F. Jerne and the Origin of the Selection Theory of Antibody Formation," Journal of the History of Biology, 1994, 27: 481-530.

phagocytes then transport them to clusters of antibody-generating cells where they stimulate the production of more like antibodies.[81] Initially, Jerne's theory was not well-received.[82] It solved the problem of immunological memory, but violated the central dogma of molecular biology, which holds that instructions for the manufacture of all cellular products are genetic. In 1957, Frank MacFarlane Burnet rescued Jerne's theory by proposing that the antigen-antibody complexes did not directly influence internal cellular processes, but rather triggered the proliferation of lymphoid cells that were genetically programmed to secrete the specific antibodies required.[83] The subsequent broad acceptance of Burnet's 'clonal selection' theory launched a revival of biological thinking in immunology, and, as Anne Marie Moulin reports, established, simultaneously, conceptual and institutional foundations for the contemporary idea that immunology consists in the study of, not just discrete cells, molecules, and biochemical interactions, but an integrated, organized biological system – the immune system.[84]

---

[81] N.K. Jerne, "The natural selection theory of antibody formation," Proceedings of the National Academy of Science, 1955, 41: 849-857.

[82] Jerne's work was eventually honored, in 1984, with a Nobel Prize in physiology and medicine, certainly less for the substantive details of the biological processes that it outlined than for its revolutionary character and its historical role in transforming the discipline of immunology.

[83] F.M. Burnet, "A modification of Jerne's theory of antibody production using the concept of clonal selection," Australian Journal of Science, 1957, 20: 67-68.

[84] Anne Marie Moulin, "The Immune System: A Key Concept for the History of Immunology," History and Philosophy of the Life Sciences, 1989, 11: 221-236. Others have noted that the 'biological revolution' – the Kuhnian 'paradigm shift' – that swept immunology in the 1960s was a social as well as conceptual phenomenon characterized by new patterns of communication and new associations between immunologists and researchers in other areas of biology and medicine. See Ilana Löwy, "The Strength of Loose Concepts – Boundary Concepts, Federative Experimental Strategies, and Disciplinary Growth: The Case of Immunology," History of Science, 1992, 30: 371-396; Thomas Söderqvist and Arthur M. Silverstein, "Participation in Scientific Meetings: A New Prosopographical Approach to the

In the 1960s, immunology blossomed and empirical studies in many new areas began to reveal the full complexity of immunological functions.[85] Investigations extending the dominant immunochemical research programs of the 1940s and 1950s moved toward the molecular study of immunogenetics, and came to represent just a small portion of the burgeoning activity in the field. In addition to opening new avenues of research on the cellular bases of antibody production, specificity, and diversity, the biological turn redirected immunologists' attention to processes of cell-mediated immunity and immunoregulation, including self/not-self recognition, the phenomenon of autoimmunity, and autoimmune disorders.[86] The universe of objects recognized as immunological increased dramatically during the 1960s. Among the new additions were novel classes of antibodies, lymphocytes, and other immune system cells with differentiated functions in immune processes, and a wide array of additional immune system components, including numerous complement proteins.

Disciplinary History of Science – The Case of Immunology, 1951-1972," Social Studies of Science, 1994, 24: 513-548.

[85] Recent works in the history and sociology of immunology have supplemented 'theory-centric' stories of this disciplinary transition, and earlier trends, with attention to the ways in which material practices have shaped the production of new immunological knowledge. See, for example, Alberto Cambrosio and Peter Keating, "A Matter of FACS: Constituting Novel Entities in Immunology," Medical Anthropology Quarterly, 1992, 6: 362-384; Peter Keating, Alberto Cambrosio, and Michael Mackenzie, "The Tools of the Discipline: Standards, Models, and Measures in the Affinity/Avidity Controversy in Immunology," pp. 312-354 in The Right Tools for the Job: At Work in Twentieth-Century Life Sciences, eds. Adele E. Clarke and Joan H. Fujimura, Princeton, NJ: Princeton University Press, 1992; G.J.V. Nossal, "The Coming of Age of Clonal Selection Theory," pp. 41-72 in Immunology 1930-1980: Essays on the History of Immunology, ed. Pauline Mazumdar, Toronto: Wall & Thompson, 1989; Nicolas Rasmussen, "Freund's Adjuvant and the Realization of Questions in Postwar Immunology," Historical Studies in the Physical and Biological Sciences, 1993, 23: 337-366; Arthur M. Silverstein, "The Heuristic Value of Experimental Systems: The Case of Immune Hemolysis," Journal of the History of Biology, 1994, 27: 437-447.

[86] Scott H. Podolsky and Alfred I. Tauber, The Generation of Diversity: Clonal Selection Theory and the Rise of Molecular Immunology, Cambridge, MA: Harvard University Press, 1997; Alfred I. Tauber, "Frank Macfarlane Burnet and the Immune Self," Journal of the History of Biology, 1994, 27: 531-574.

Only after the biological turn in immunology in the 1960s did many familiar (to practitioners) terms and objects of research – like granulocytes, mast cells, effector cells, suppressor cells, natural killer cells, helper cells, memory cells, light chains, heavy chains, idiotypes, cytokines, lymphokines, interferon, and major histocompatibility complex, for example – become part of the regular disciplinary vocabulary.

A key premise of the clonal selection theory is the idea that immunoglobulin secreting lymphocytes produce specific antibodies of one type only. Immunologist G.J.V. Nossal has chronicled the series of experiments that practitioners in the field now generally accept as a confirmation of this hypothesis, and described how research in molecular immunogenetics has provided additional empirical support for clonal selection theory and the 'one cell/one antibody' idea by outlining the genetic mechanisms that account for antibody diversity.[87] Nossal states that "quantitative and objective measurement of each [antibody producing] cell's fine specificity aided the cause of those postulating a random generator of diversity...and was also an early harbinger of the monoclonal antibody revolution."[88] The 'monoclonal antibody revolution' began in England, but soon arrived in San Diego, where it launched the city's biotech industry. In 1975, German cell biologist Georges Köhler and Argentine biochemist César Milstein, in Milstein's Medical Research Council lab at Cambridge, developed 'hybridoma technology,' the fusion of antibody producing genes from

---

[87] G.J.V. Nossal, "The Coming of Age of Clonal Selection Theory," pp. 41-72 in Immunology 1930-1980: Essays on the History of Immunology, ed. Pauline Mazumdar, Toronto: Wall & Thompson, 1989.

[88] Nossal, "The Coming of Age of Clonal Selection Theory," p. 41.

mammalian B-lymphocytes with myelomas (malignant bone marrow cells) that replicate indefinitely. The pair were conducting studies in cellular genetics. Their first interest in proteins produced by fused myelomas was the utility of these substances in the analysis of rates of somatic mutation and the generation of antibody diversity. They observed, in addition, however, an odd unintended result of their work: the particularized genetic codes and 'immortality' of their new hybrid cell lines made possible for the first time the production of large quantities of monoclonal antibodies.[89]

Monoclonal antibodies are identical and highly specific immunoglobulins; they bind to a particular antigenic determinant, or epitope – a definite molecular and chemical configuration on the surface of a particle or substance that elicits an immune response. Monoclonals are homogeneous because they are products of clones, i.e., cells descended from a single antibody producing lymphocyte. And, because myeloma hybrid clones are immortal, they can produce antibodies continuously. Prior to this development, antibodies used in research and medicine had either to be purified from polyclonal antisera harvested from immunized animals, mixtures that contain many different types of antibodies, or by laborious methods that involved repeatedly isolating specific lymphocytes that could not be maintained in tissue cultures.[90]

---

[89] G. Köhler and C. Milstein, "Continuous cultures of fused cells secreting antibody of predefined specificity," Nature, 1975, 256: 495-497. For a history of the diffusion of this technology, see Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995; ch. 1, especially.

[90] Even when polyclonal mixtures are purified, that is, screened for immunoglobulins specific to a particular antigen, the surviving antibodies remain heterogeneous. They possess different specificities and varying degrees of crossreactivity and affinity for the target. This is so because different antigens may possess binding sites that are similar in chemical structure, and the surface of any given antigen displays many different epitopes.

Hybridoma technology permitted the efficient and inexpensive production of standardized, uniformly specific antibodies. Monoclonals have proven to be enormously useful as biological reagents in a wide range of scientific and medical applications. Because they can hone in on specific targets with precision, they are used to monitor biological and chemical processes of many different kinds, and to diagnose and combat human diseases.

The 'monoclonal antibody revolution' eventually became part of an industrial and organizational revolution – the formation of entrepreneurial biotech start-ups. Once recognized, the promise of hybridoma technology for the manufacture of diagnostics and therapeutics in huge, untapped medical markets spurred an influx of capital to a number of such ventures in the late 1970s and early 1980s. Hybritech was the first. It was San Diego's first biotech company, and it was also the world's first commercial undertaking dedicated to the industrial development of hybridoma technology and the manufacture of monoclonal-based medical products. With the formation of this company in San Diego, the new 'biologized' science of immunology went into business. The histories of hybridoma technology, monoclonal antibodies, monoclonal companies, monoclonal products, and the birth of the biotechnology industry in San Diego share at least one common element. All were made scientifically possible by the biological renaissance in immunology, and within this intellectual and technical disciplinary shift, the synthesis of experimental investigations in genetics, cell biology, and the cellular processes of antibody formation.

As many historians and sociologists of science have lately pointed out, the social organization and politics of scientific disciplines shape the particular ways in which bodies of scientific knowledge and the technical capacities of the sciences are extended. Within any given field, researchers share common intellectual orientations, conceptual frameworks, and traditions of material practice. Their private investigations are not conducted in isolation, but within networks of formal and informal communication – 'invisible colleges' through which they are connected to colleagues who are scattered, in many contemporary cases, all around the world, and through which they are kept abreast of distant practices and developments in their specific fields of inquiry.[91] These networks serve as channels of resource distribution. The people, knowledge, skills, and tools that scientists employ to make discoveries and invent new technologies circulate within them. Of course, these networks are also arenas of competition. Within them, information and know-how are commodities, and the reward structures of the sciences provide incentives for secrecy and the establishment and protection of proprietary rights. But if scientific communication ceases altogether, then so does scientific progress.

Science is a collective practice and the character of new products in the sciences – facts, theories, standards, techniques, etc. – always reflect the social organization and the histories of these fields of activity. When knowledge and skill

---

[91] The phrase 'invisible college' was coined by Diana Crane. See Diana Crane, Invisible Colleges, Chicago: University of Chicago Press, 1972. For an ethnographic analysis, see Robert E. Kraut, Carmen Egido, and Jolene Galegher, "Patterns of Contact and Communication in Scientific Research Collaborations," pp. 149-172 in Intellectual Teamwork: Social and Technological Foundations of Cooperative Work, ed. Jolene Galegher, Robert E. Kraut, and Carmen Egido, Hillsdale, NJ: Lawrence Erlbaum Associates, 1990. For a general discussion of recent historical and sociological works on scientific networks, see chapter one, pp. 38-73.

are compartmentalized, distributed, and transmitted in particular ways, certain horizons of possibility and avenues of progress are created and defined, as are barriers to advancements in a range of possible alternative directions. As the brief potted histories of molecular biology, molecular genetics, and immunology above illustrate, the technical development of new bioscientific tools followed the social development of new patterns of interdisciplinary communication. The scientific discoveries and inventions that led to the creation and commercialization of new biotechnologies in San Diego and elsewhere emerged from within definite social and historical processes. These technical advances were bound up with the organizational and political constitution of the life sciences in the 20th century. As the rest of this study will show, the scientific entrepreneurs who appeared in San Diego during the late 1970s were prepared for their tasks by participating in these processes in various ways.

SCIENCE AND MONEY

Just as laboratory investigations are not conducted in a social vacuum, neither are the larger patterns of collective activity that comprise scientific disciplines. The members of scientific communities go about their business within broader institutional settings and processes. The reward structures, competitive dynamics, and patterns of communication that characterize disciplinary work take forms that reflect their social and historical contexts. As most historians of science are now wont to insist, disciplinary histories that fail to address the institutional surroundings of the sciences are incomplete. Scientific work and scientific progress, the historians say, are impacted, not only by events taking place in test tubes, petri dishes, particle accelerators, scientific meetings, and so on, but also by 'extrascientific' events that

may unfold far afield from the laboratory and other regular haunts of practicing scientists. The remarkable technical strides taken by the life sciences in the middle and late 20th century originated, in a sense, with conditions and happenings in larger institutional environments. These advances were generated, in part, by 'external' forces that worked to push bioscientific inquiries in certain directions rather than others. They were influenced significantly by, among other things, the historical trajectories of the academic research institutions that have traditionally housed the life science disciplines, and shifting patterns of funding for biological and biomedical research from private foundations, government agencies, and industry.

Naturally, most practicing scientists are acutely aware of the economics of science. In the life sciences, as in other fields, success usually depends as much on effective grantsmanship and organizational skill as it does on conceptual insight, creativity, or technical facility demonstrated at the lab bench.[92] In universities, scientific positions and spaces are reserved for those who can attract extramural funding to support their inquiries, and scientific agendas are often shaped by this dependence of scientists on outsiders. Paths of research in the sciences are typically defined by negotiations of interest between scientific practitioners and their patrons. A knack for knowing 'what's hot and what's not' – that is, understanding what kinds of grant proposals are likely to be funded and what kinds will likely end up in a shredder – is a valuable scientific talent to possess.

---

[92] For this reason, talk about economic (or social, cultural, or political) factors 'external' to scientific work is, in the strictest terms, misconceived. For a discussion of the point as it bears on historians' academic analyses, see Steven Shapin, "Discipline and Bounding: The History and Sociology of Science as Seen Through the Internalism-Externalism Debate," History of Science, 1992, 30: 333-369.

As anthropologist Joan Fujimura points out, in order to conduct their investigations, researchers are often obliged, of necessity, to jump on 'scientific bandwagons.' The history of biological and biomedical research in the 20th century is a history of such bandwagons.[93] The technical development of the life sciences during this time depended, of course, on the availability of funds to open and maintain laboratories and programs of research; the direction of this development was influenced by the interests of benefactors and by the good fortune and skills (both scientific and social) of researchers in particular areas of inquiry that enabled them to win out in competitions for contracts and grants. The molecular biologists and molecular geneticists who laid the groundwork for later biotechnological developments did so by persuading others that the future of science lay in the direction they were headed, by aligning their interests with those holding the money bags, and by turning molecular biology and molecular genetics into 'scientific bandwagons.'

The initial rise of the molecular paradigm in biology, as many scholars have detailed, was underwritten by generous financial support and organizational direction from private foundations. The role of the federal government was relatively limited.[94] Among the principal private sponsors were the Carnegie Foundation and the Rockefeller Foundation. The latter, under the direction of Warren Weaver in the 1930s, played a particularly instrumental role in the formation and development of

---

[93] Fujimura provides an empirical description of the scientific, social, and institutional processes constituting one such historically important biomedical bandwagon – the proliferation of oncogene studies in cancer research. See Joan H. Fujimura, Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer, Cambridge, MA: Harvard University Press, 1996; and "The Molecular Biological Bandwagon in Cancer Research: Where Social Worlds Meet," Social Problems, 1988, 35: 261-283.

molecular biology.[95] Weaver promoted and funded research at the intersection of physics and biology, and was content to let researchers following other paths of inquiry fend for themselves as best they could without the help of his organization. Molecular biology benefited at the expense of more traditional approaches. In the post-war era, the federal government, through existing agencies like the National Institutes of Health and the newly-formed National Science Foundation, assumed a vastly expanded role in the financing, administration, and coordination of the life sciences.[96] A massive influx of federal dollars in the 1950s transformed biological and biomedical research into 'Big Sciences,' and into a machine that became increasingly focused on investigations into the molecular fundamentals of biological processes.[97]

The floodgates opened wide when Congress began to increase subsidies for the National Institutes of Health. The increases began in 1955 and continued for more than a decade. In 1967, NIH funding of biomedical and basic biological research

---

[94] Victoria Harden, Inventing the NIH: Federal Biomedical Research Policy, 1887-1937, Baltimore, MD: Johns Hopkins University Press, 1986.

[95] See E. Richard Brown, Rockefeller Medicine Men: Medicine and Capitalism in America, Berkeley, CA: University of California Press, 1979; Robert E. Kohler, "The Management of Science: Warren Weaver and the Rockefeller Foundation Program in Molecular Biology," Minerva 14: 249-293; and Partners in Science: Foundations and Natural Scientists, 1990-1945, Chicago: University of Chicago Press, 1991. Lily E. Kay contends that the Rockefeller Foundation supported a definite social as well as purely scientific agenda – eugenics. See Lily E. Kay, The Molecular Vision of Life: Caltech, the Rockefeller Foundation, and the Rise of the New Biology, New York: Oxford University Press, 1993.

[96] Milton Lomask, A Minor Miracle: An Informal History of the National Science Foundation, Washington, D.C.: National Science Foundation, 1976.

[97] Peter Galison and Bruce Hevly, eds., Big Science: The Growth of Large Scale Research, Stanford, CA: Stanford University Press, 1992. The empirical studies in this book examine the formation of big physics, but the size of organizations and investigative teams in biological and biomedical research followed the same general pattern when funds became available to expand them.

reached a high-water mark (in terms of adjusted constant dollars) when it doled out over $1 billion to bioscientists across the nation.[98] Soon after, in 1971, President Richard Nixon declared a 'war on cancer,' signed into law the National Cancer Act (with the approval and assistance of unlikely political ally Sen. Edward Kennedy), and promised that the American biomedical research machine would vanquish the disease within five years.[99] Following this legislation, there began to appear, in federal grant proposals for biological research of all kinds, statements on the relevance of planned investigations to the understanding of cancer mechanisms. Critics of the 'war on cancer' argued that many of these rationales were flimsy, and that the initiative encouraged much 'junk science,' but, in any event, billions of dollars found their way to the frontlines in biological laboratories, and they became increasingly concentrated in the area of molecular genetics.[100] The remarkable series of scientific breakthroughs that culminated in the invention of biotechnologies were largely financed by the

---

[98] National Institutes of Health, Extramural Trends FY 1972-1981, Bethesda, MD: National Institutes of Health.

[99] Joan H. Fujimura, Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer, Cambridge, MA: Harvard University Press, 1996; Ralph Moss, The Cancer Industry: Unraveling the Politics, New York: Paragon House, 1989; Richard Rettig, Cancer Crusade: The Story of the National Cancer Act of 1971, Princeton, NJ: Princeton University Press, 1977; Kenneth E. Studer and Daryl E. Chubin, The Cancer Mission: Social Contexts of Biomedical Research, London: Sage, 1980.

[100] The 'war on cancer' was controversial and its merits are still debated. Opponents argued that bioscientific and biomedical advances usually come serendipitously from basic investigations into fundamental biological processes. Progress in science, they maintained, cannot be planned. Others have defended the initiative, responding that, although no cancers were cured, the focused research yielded valuable knowledge and techniques on which future inquiries can build. For a recent summary of the debate, see Rachel K. Sobel, "Volleys in the Cancer War: Has the Thirty Year Enterprise Been Wrongheaded From the Start?" U.S. News & World Report, June 18, 2001.

federal government and monies earmarked for the 'war on cancer.'[101] The technical advances that led eventually to the creation of a new sector within the pharmaceutical industry thus have their origins in broad national commitments to the promotion of basic science and medical research after World War II. Molecular biology can thank the largess of American philanthropists for its initial success; the biotechnology industry owes additional and considerable debts to American taxpayers, and the political will and sheer economic power of the United States in the 20th century.

ON THE SHOULDERS OF A GIANT

With the formation of San Diego's centers of scientific research during the 1960s and into the 1970s, the city went from being nowhere in particular on the map of American higher education and international science and technology to being one of the strongest centers of gravity in the world for scholars, scientists, and engineers. Today, living in or frequenting San Diego are seven living Nobel laureates (one, perhaps mostly because he is a dedicated surfer),[102] some seventy members of the eminent National Academy of Science, and recipients of prestigious scientific medals, prizes, and citations numbering in the hundreds. In the span of little more than a decade, San Diego had become fortuitously prepared to take advantage of opportunities in the emerging global 'knowledge' economy – although, at the time, the character of the coming environment for trade and invention was just beginning to

---

[101] Martin Kenney, Biotechnology: The University-Industrial Complex, New Haven, CT: Yale University Press, 1986, ch. 1; Ginzberg, Eli, and Anna B. Dutka, The Financing of Biomedical Research, Baltimore, MD: Johns Hopkins University Press, 1989.

[102] See Kary Mullis, Dancing Naked in the Mind Field, New York: Vintage Books, 1998.

dawn on analysts[103] – and to rescue itself later from economic decline in the 1990s following the end of the Cold War.

The foundings of the city's biological research organizations – including notably, the Scripps Research Institute, the Salk Institute for Biological Studies, and the life sciences departments and the School of Medicine at UCSD – were important developments in the prehistory of San Diego's biotechnology industry. They were the magnets that drew to San Diego many of the persons who would, from the late-1970s on, become the city's bioscientific entrepreneurs. They were the gateways through which these entrepreneurs passed on their way to founding new companies and a new kind of economic activity in town. They were the places in which a body of world-class bioscientific expertise became localized, and in which teams of researchers invented many of the new technologies that scientific entrepreneurs then transferred to commercial ventures in nearby parts of the city for further development as products in pharmaceutical markets.

This concentration of bioscientific expertise in San Diego can perhaps be called something like a necessary 'cause' of later developments in the biotechnology industry, but not a sufficient one, for things could have turned out very differently, and many other events had to take place, in addition, and many other historical processes had to work themselves out, in order for the biotechnology industry to take shape in San Diego as it did. The mere presence of research institutions in the city does not explain what people did within them or what they did as they moved beyond the walls

---

[103] See, for example, Daniel Bell, The Coming of Post-Industrial Society: A Venture in Social Forecasting, New York: Basic Books, 1976 [1973].

of their laboratories. What San Diego's scientific entrepreneurs could do in order to establish the biotechnology industry in the city was partially determined, first of all, by prior developments in the biological sciences. Naturally, biotechnologies did not materialize in San Diego, or anywhere else, unaccompanied by long technical and social histories. When invented, these new techniques represented extensions of established bodies of knowledge and experimental practices in various life science disciplines. Many biotechnologies have been forged in San Diego laboratories, and in these places exclusively (and documenting such exclusivity and securing patent rights has usually been a prerequisite for commercialization), but workers in these labs were immersed in traditions of technical work and technical thinking that characterized the life sciences at large. New biotechnologies were built 'on the shoulders of a giant' – the community of life scientists, and the individuals who were responsible, collectively, for discoveries and inventions that came before.

V. LIFE SCIENCE AND INDUSTRY

Chance does nothing that has not been prepared beforehand.

Alexis de Tocqueville

THE COMMERCIALIZATION OF SCIENCE

After World War II, U.S. government investments in science and technology grew substantially. As part of this boom, federal support of academic biomedical research steadily increased through the mid-1970s. When the health of the American economy deteriorated toward the end of the decade, however, government funding began to stagnate and decline.[1] Feeling the pinch, universities began to look elsewhere for financial assistance, and they became much more receptive to partnerships with industry as means of subsidizing research. The ready availability of federal funds in better economic times had permitted universities to distance themselves from private corporations, but when sources of government money began to dry up, many institutions began actively to pursue collaborations with business organizations, and to adjust administrative policies in order to accommodate these new relationships.[2] For their part, American industrialists were eager to purchase technical assistance from academic scientists as a means of arresting the general decline of U.S. economic competitiveness (and, in the case of the pharmaceutical business, in

---

[1] Eli Ginzberg and Anna B. Dutka, The Financing of Biomedical Research, Baltimore, MD: Johns Hopkins University Press, 1989.

[2] See Roger L. Geiger, Research and Relevant Knowledge: American Research Universities Since World War II, New York: Oxford University Press, 1993. The trend has continued in California, as elsewhere. See Office of the President, University of California, "Guidelines on University-Industry Relations," May 1989; University and External Relations, University of California Office of the President, "UC Means Business: The Economic Impact of the University of California," Oakland, CA: UC Office of the President, 1995.

particular, because rates of innovation in new product development had begun to flag).[3] American faith in the power of science remained undiminished, and gossip about the arrival of a new post-industrial 'knowledge-based' economic order was beginning to circulate. Federal support for biomedical research would resume an upward climb in the mid-1980s, but as a percentage of total university research budgets, government contributions continued to taper off. Industrial funding of academic science rose dramatically in the 1980s. In 1980, commercial entities contributed $350 million to research in American universities. By 1988, the figure had risen to $816 million.[4] Corporate support for university-based biological and biomedical science in the U.S. has since continued to increase.[5]

Shifts in federal science and economic policies in the late-1970s and early 1980s also encouraged the privatization of research and the development of more extensive ties between universities and industry.[6] An important piece of legislation reflecting Washington's new line was the Bayh-Dole Act of 1980. The Bayh-Dole Act assigned ownership of patents on inventions developed in academic settings with federal monies to universities rather than the funding agencies. These property rights generated financial incentives for academic institutions to capitalize on research by

---

[3] Alfonso Gambardella, Science and Innovation: The U.S. Pharmaceutical Industry in the 1980s, Cambridge: Cambridge University Press, 1995, ch. 5.

[4] OECD, University-Enterprise Relations in OECD Member Countries, Paris: OECD, 1990.

[5] Enriqueta C. Bond and Simon Glynn, "Recent Trends in Support for Biomedical Research and Development," pp. 15-38 in Sources of Medical Technology: Universities and Industry, eds. Nathan Rosenberg, Annette C. Gelijns, and Holly Dawkins, Washington, D.C.: National Academy Press, 1995.

[6] Bruce L.R. Smith, American Science Policy Since World War II, Washington, D.C.: Brookings Institution, 1990.

pursuing with greater vigor the licensing and commercialization of new technologies invented on their premises. The rationale behind this policy transformation was that the privatization of research would speed and expand the transfer of knowledge and technologies from academic institutions to industry, compressing the time in which economic and technological benefits would be derived from public investments in the sciences.[7] The U.S. Congress decided, in effect, to withdraw the federal government, partially, from the business of technological innovation, and to remove bureaucratic barriers to interactions and collaborations between universities and private corporations.

As well as influencing the governance of academic institutions, the transformation in relations between universities, industry, and the state soon impacted work conducted at laboratory benches throughout the country. University faculty began conducting more contract research and engaging in more collaborative projects with industrial scientists than in the past. Academic institutions began developing new kinds of on-campus centers dedicated to applied research and technological development. Reflecting conditions of support from corporate sources, research agendas in universities became increasingly set by industrial concerns, and more individual research projects were directed toward definite practical ends.[8] This remodeling of scientific inquiry was controversial from the beginning.[9] Many critics

---

[7] See Gary W. Matkin, Technology Transfer and the University, New York: Macmillan, 1990.
[8] For a summary of University of California policies encouraging the trend, as an example, see University of California, "President's Initiative for Industry-University Cooperative Research," http://www.ucop.edu/pres/industryinit.html.

[9] Early on, representatives of elite research institutions and major research corporations met to discuss possible conflicts of interest in academic-industrial partnerships. See Barbara Culliton, "Pajaro Dunes:

have argued that progress in basic research may be impeded because corporate interests and scientific interests in the extension of bodies of knowledge may not be compatible;[10] that the commodification of knowledge may promote secrecy rather than the free exchange of information and ideas;[11] that the integrity of the sciences may be at risk because opportunities for profit will encourage scientific fraud;[12] and that the social role of the university as an institution dedicated to the universal goods of truth and knowledge is compromised when scientific research is directed toward private ends and knowledge becomes proprietary.[13]

Despite these objections, and although formal commercial partnerships between university administrations and business corporations are novel developments, recent increases in industrial sponsorship of university research and the involvement of university faculty in commercial projects represent (whether for good or ill) changes in degree rather than fundamental alterations in the conduct of science.[14]

The Search for Consensus," Science, 1982, 216: 155-158. The problems they identified still have not been resolved to the satisfaction of all. The outstanding issues are examined in greater depth in the concluding chapter of this work. For a thorough, recent account in the popular press, see Eyal Press and Jennifer Washburn, "The Kept University," The Atlantic Monthly, March 2000, pp. 39-54.

[10] Andrew Webster, "University-Corporate Ties and the Construction of Research Agendas," Sociology, 1994, 28: 123-142.

[11] Michael Gibbons and Bjorn Wittrock, eds., Science as a Commodity: Threats to the Open Community of Scholars, Harlow, Essex, UK: Longman, 1985.

[12] National Academy of Sciences (Panel on Scientific Responsibility and the Conduct of Research; Committee on Science, Engineering, and Public Policy), National Academy of Engineering, and Institute of Medicine, Responsible Science: Ensuring the Integrity of the Research Process, Vol. 2, Washington, D.C.: National Academy Press, 1993.

[13] Sheila Slaughter and Larry L. Leslie, Academic Capitalism: Politics, Policies, and the Entrepreneurial University, Baltimore, MD: Johns Hopkins University Press, 1997.

[14] Sociologists have worked for the past thirty years to dispel the myth of 'pure science.' Against suggestions that service to corporate interests will corrupt academic inquiry, a large body of empirical sociological research indicates that scientific work is rarely, if ever, motivated solely by curiosity or love of truth, and that, despite commonplace talk about 'ivory towers,' academic communities and

From the time of the establishment of the research university as an American social institution in the late 19th century, academically trained and employed chemists, physicists, and engineers have conducted 'applied' research and participated in industrial projects.[15] University faculty in these fields have long offered their services as consultants and performed contract research, and, occasionally, they have started their own companies in order to develop inventions commercially (although, until recently, with a few notable exceptions, MIT and Stanford, for example, this kind of entrepreneurial activity was not encouraged).[16] Late shifts in science funding, federal

---

academic knowledge production have never been effectively insulated from broader social interests and cultural prejudices. See Daniel Lee Kleinman and Steven Peter Vallas, "Science, Capitalism, and the Rise of the 'Knowledge Worker': The Changing Structure of Knowledge Production in the United States," Theory and Society, 2001, 30, 4: 451-492. Scientists may, in fact, be motivated by curiosity and love of truth, and some may take academic ideals seriously, but before the recent explosion of corporate funding of projects in the life sciences, the academic racket was no purer and no less competitive than the world of commerce, even if its principal currency was prestige derived from priority in discovery and publication rather than monetary profit. For a summary of the sociological view on the interested character of science, see Barry Barnes and David Edge, "The Organization of Academic Science: Communication and Control," pp. 13-20 in Science in Context: Readings in the Sociology of Science, eds. Barry Barnes and David Edge, Milton Keynes: Open University Press, 1982.

[15] Roger L. Geiger, To Advance Knowledge: The Growth of American Research Universities, New York: Oxford University Press, 1986; Christopher Jenks and David Riesman, The Academic Revolution, Garden City, NY: Doubleday, 1968. Recent scholarship in history and sociology of science has challenged the assumption that 'basic' research is conducted only in academic settings. For a discussion on the character of, and the relations between, industrial research and university-based science, see Michael Aaron Dennis, "Accounting for Research: New Histories of Corporate Laboratories and the Social History of American Science," Social Studies of Science, 1987, 17: 479-518. Dennis rejects essentialist renderings of scientific and technological projects that include dichotomous categorizations of 'science' and 'technology,' and 'pure' and 'applied' science. He points out that much new knowledge has been generated in industrial labs. For case studies that document it, see David A. Hounshell and John Kenly Smith, Jr., Science and Corporate Strategy: DuPont R&D, 1902-1980, Cambridge: Cambridge University Press, 1988; Leonard S. Reich, "Edison, Coolidge, and Langmuir: Evolving Approaches to American Industrial Research," Journal of Economic History, 1987, 47: 341-351; Leonard S. Reich, The Making of American Industrial Research: Science and Business at GE and Bell, 1876-1926, Cambridge: Cambridge University Press, 1985; and George Wise, Willis R. Whitney, General Electric, and the Origins of U.S. Industrial Research, New York: Columbia University Press, 1985.

[16] See Henry Etzkowitz, "Enterprises from Science: The Origins of Science-Based Regional Economic Development," Minerva, 1993, 31: 326-360; and "The Making of an Entrepreneurial University: The Traffic Among MIT, Industry and the Military, 1860-1960," in Science, Technology, and the Military,

science policy, and university administration altered the circumstances of the life sciences more than those of chemistry, physics, or engineering. Until the late 1970s and early 1980s, biology was the most academic of the sciences. There were relatively few opportunities for contract research or consulting available to members of academic biology departments. The appearance of new biotechnologies in the life sciences – techniques developed largely on nickels donated by the government and non-profit organizations – changed this situation rapidly and dramatically. The development of new technical capacities in the biosciences coincided with, and contributed to, the formation of more extensive university-industry ties, and the evolution of the university as a social institution in the late 1970s. These happenings worked contemporaneously to remold the social character of the life sciences.

Before the advent of new biotechnologies, the life sciences were oriented primarily toward 'basic' research – that is, they tended to reward 'fundamental' discoveries, and were generally less concerned with exploring 'practical' applications of scientific knowledge and techniques (i.e., those extrinsic to the ends of scientists qua academicians). Apart from the general assumption that advances in basic biological science would eventually inform the practice of medicine, there were, before the 1970s, very few ideas in the air about how cutting-edge biological research could be applied to any specific practical ends. Biotechnological inventions quickly changed this circumstance. They enabled scientists to begin reengineering life processes. Progress in biological research soon began to issue directly from

---

eds. Everett Mendelsohn, Merritt Roe Smith, and Peter Weingart, Dordrecht, Netherlands: D. Reidel, 1988.

applications of these new techniques to the practical problems of medicine and other spheres of activity. The line separating 'basic' and 'applied' inquiries was blurred, and many researchers found that, in order to move forward into areas of inquiry opened up by the new techniques, the life sciences had to be remodeled organizationally. Biotechnologies had originally emerged from research conducted at the intersections of scientific disciplines – biology, chemistry, physics, and medicine. This work was performed mostly in academic settings. Still, the traditional organization of universities into departments and schools discourages cross-disciplinary communication, cooperation, and resource distribution. When the biosciences arrived at a point where solutions to many of their emergent problems and challenges lay with the further interdisciplinary development of new techniques, organizational boundaries stood as barriers to the kinds of progress that many practitioners wished to pursue.

The ongoing transformation of research universities in the 1970s influenced the strategies that academic biotechnologists adopted at the time in order to solve these kinds of organizational problems. When life scientists began developing their powerful new tools for manipulating biological processes, they did so in the midst of an institutional transition. As universities cast about for new means of sustaining themselves and their research missions in hard economic times, bioscientists were presented with a related range of opportunities for restructuring their collective practices in alternative organizational forms. Prior to the introduction of biotechnologies, the entrepreneurial and organizational skills of life scientists were put to use mostly within universities and non-profit research institutions, building

academic empires and attracting grants from federal agencies and private foundations. By the time biotechnologies had been firmly established as material bases for further progress in the life sciences, an entirely new constellation of opportunities had come into view. On the campuses of elite American research universities in the 1970s, communications and interactions between academics and industrialists were increasing, and venture capitalists had started to drop by for visits, snooping around for chances to establish the next Hewlett-Packard, Digital Equipment Corporation, Cypress Semiconductor, or Intel. In this environment, bioresearchers were exposed to new possibilities for financing and organizing their work by commercializing their new inventions.

Commerce was alluring to top bioscientists because private investments seemed a viable alternative to federal funding, and because research in industrial settings posed few built-in obstacles to interdisciplinarity. In fact, the project-focused character of industrial work facilitates interdisciplinary communications and interactions. Moreover, commercialization offered researchers chances to pursue their work away from the byzantine politics of the academy, unburdened by teaching responsibilities, and freed from the seemingly endless task of writing up grant proposals for review by federal bureaucrats. Finally, as venture capitalists promised many of the scientists that they courted, if things went well with new companies, everybody involved could get rich. There were plenty of new computer, semiconductor, and software millionaires walking around Silicon Valley and along Route 128 in Boston, why not biotech millionaires, too? Conditions both within and without universities in the late 1970s and early 1980s thus encouraged elite academic

life scientists with technologies that could be made proprietary to explore possibilities for developing their inventions extramurally, and some of the more adventurous elected to become involved in private entrepreneurial ventures.

The appearance of new biotechnology firms also prompted researchers situated on the lower rungs of the academic ladder to consider whether industry might not offer greener pastures. Often, these deliberations were born of necessity, for disruptions and contractions in funding and university budgets in the late 1970s had overheated competition in markets for academic research jobs. It was also true, however, that compelling scientific and technical challenges were now to be found in industry as well in academic settings, and, by and large, well-known and well-respected academics had put them there. The scientific legitimacy of commercial biotechnology was never really in question, even if the professional status of industrial molecular biologists was at first uncertain. Many young bioscientists decided to leave their academic posts in order to pursue alternative careers in the biotechnology business. For a short period when this business was first taking shape, there was something of a stigma attached to industrial work vìs-a-vìs the prestige of academic appointments, and university faculties may still sometimes cultivate attitudes of academic elitism.[17]

---

[17] Between 1977 and 1991, the percentage of life science Ph.Ds employed in industry five-to-eight years after receiving the terminal degree jumped from 11.4 to 25.4. See Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, Institute of Medicine, Reshaping the Graduate Education of Scientists and Engineers, National Academy Press, 1995, p. 37; see also Martin Kenney, Biotechnology: The University-Industrial Complex, New Have, CT: Yale University Press, 1986. For personal testimonies and stories of individual bioscientists who have elected to cast their lots with industrial concerns, see Arthur Kornberg, The Golden Helix: Inside Biotech Ventures, Sausalito, CA: University Science Books, 1995; Virginia Morell,"The Rewards of Intellectual Bigamy," The Scientist, 1989, 3: 6; Paul Rabinow, Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press, 1996; Robert Teitelman, Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology, New York: Basic

For the most part, though, academic researchers do not dishonor themselves by accepting scientific positions in commercial biotech ventures.

The origins of these various trends and happenings that preceded or constituted the emergence of the U.S. biotech industry can be located, partially, in broader social processes that came together to produce new institutional environments and conditions in the 1970s. Technical and social developments unfolding on national and international scales combined to transform the domestic economy, U.S. government science policy, patterns of funding for scientific research, American universities, and the sciences themselves, to create the historically specific context in which bioentrepreneurs and biotechnologists would operate regionally and locally in places like San Diego. This confluence of institutional processes and developments prepared life scientists for new social roles, and shaped an environment in which some them would invent and refine a new kind of practice, the transfer of bioscientific knowledge and techniques to new entrepreneurial start-up companies in the pharmaceutical trade.

Technical progress in the biological sciences through the mid-1970s was largely underwritten by the federal government and philanthropic foundations. Thereafter, various social and economic processes began to transform the American research university as a social institution. The circumstances of academic bioscientists were naturally transformed as well. During the 1970s, elite schools and centers of scientific research in the U.S. became understood, increasingly, by persons and groups situated within and around them, as 'handmaidens to industry' or 'drivers of economic

---

Books, 1989, ch. 2, and Barry Werth, The Million Dollar Molecule: One Company's Quest for the Perfect Drug, New York: Simon & Schuster, 1994.

progress' (university administrators are evidently fonder of the latter phrase). Academicians in many different fields of science and engineering began to pursue closer ties with private corporations and to engage in new forms of interaction with these entities. As affiliations and alliances of this sort proliferated and deepened, universities became suspended in dense webs of organizational interdependencies with industrial concerns. The academic production of knowledge and the commercial production of market goods, formerly housed in separate rooms with relatively few points of contact, gradually became more interconnected and intertwined. Industry became more reliant on 'inputs' from universities and university scientists, while universities became more dependent on corporate investments in academic research. Industrialists and university administrators defended the new partnerships by insisting that they would expand, improve, and enrich both academic knowledge-making and industrial production. In the 1970s, knowledge, money, and materials started flowing in greater volumes through formal and informal social links spanning the academic-industrial divide.

The invention of new methods for manipulating life processes coincided with these institutional transformations and prevented biological research from languishing as federal funding began to contract. As universities adapted to their new financial environments, biological scientists, too, felt increasing pressure to secure extramural funding from private sources. At the same time, they were exposed to new models for establishing and managing academic empires with corporate dollars, and for commercializing new findings and techniques as well – those that university faculty in other departments and schools were devising. Researchers in physics, chemistry, and

engineering had already begun multiplying and amplifying their links with industrialists and venture capitalists. Bioscientists soon followed suit, and, as they found markets for their new biotechnological inventions, their projects and programs likewise became increasingly intertwined with private and corporate ends. They began increasingly to rely on private and corporate funding to sustain their inquiries. This trend helped to create the context in which new biotechnologies would be transferred from academic labs to new entrepreneurial start-ups. It also altered fundamentally the future prospects of biotechnical progress and biotechnical work. Once new biotechnologies were conceived, 'reduced to practice,' and delivered to industry for commercial development, their historical trajectories, and the careers of the scientific entrepreneurs who invented them and acted as their guardians, were shunted onto pathways defined in part by other historically and geographically distant processes and chains of events – those comprising the histories of pharmaceutical production, the medical profession, and federal drug regulation.

I am arguing in this dissertation that commercial biotechnology in San Diego during the 1970s and 1980s emerged as it did, and bioscientific entrepreneurship in this time and place took on the specific character that it did, because individual entrepreneurs working together (and at cross purposes, too) devised strategies, took actions, and made decisions that mattered. They made choices that determined historical outcomes. They did so, however, having walked onto a definite social landscape. San Diego's bioscience entrepreneurs participated, along with peers in other centers of biotech activity, in the creation of a new sector within an established industry and organizational ecology – the U.S. health care industry and surrounding

social institutions – a landscape with a history of its own. The creation of the city's cluster of biotech companies was influenced from afar (and from the past) by the peculiar technical, organizational, and competitive dynamics of the drug trade in this country. These, in turn, were shaped by the rise in prestige and authority of scientific medicine and the medical profession in American society, and the growth of the U.S. Food and Drug Administration as a powerful social institution and regulator of pharmaceutical production.

SCIENTIFIC MEDICINE AND THE PHARMACEUTICAL TRADE

In the early 19th century, American pharmaceutical production consisted mainly of apothecaries drying, crushing, roasting, and boiling the roots, stalks, leaves, flowers, and seeds of plants. Soon, however, as historian Jonathan Liebenau has detailed,[18] demographic shifts and technological and organizational innovations ushered in by the industrial revolution would set a few small, family-owned medicine-making businesses on trajectories from storefront and backroom operations toward modernization, greatly enhanced and expanded manufacturing capacities, and lengthy careers as titanic, politically powerful, and highly profitable corporations.[19] Through

---

[18] Jonathan Liebenau, Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry, Baltimore, MD: Johns Hopkins University Press, 1987. Liebenau's history focuses mainly on medicine makers operating in the city of Philadelphia, which was in the 19th century, and still is, an important national center of drug science and industry. For other accounts of the early development of the American pharmaceutical trade, see Glenn Sonnedecker, "The Rise of Drug Manufacture in America," Emory University Quarterly, 1965; Paul Starr, The Social Transformation of American Medicine, New York: Basic Books, 1982, ch. 3; John P. Swann, Academic Scientists and the Pharmaceutical Industry: Cooperative Research in the 20th Century, Baltimore, MD: Johns Hopkins University Press, 1988.

[19] Although unique in many ways, the early development of organizational structures in the pharmaceutical business paralleled those of other major U.S. industries – e.g., oil, steel, and automobiles. Business and management scholars have often compared drug manufacturing with other fields when telling of the rise of corporate capitalism and the emergence of the large, multi-divisional, vertically-structured bureaucracy as the leading form of industrial organization in the 20th century. See,

the mid and late decades of the 19th century, American markets for medicines grew, mechanization and urbanization enabled manufacturers with the necessary scale-up capital to produce their commodities in higher volumes with greater efficiency, transportation systems were vastly extended and improved, European immigrants with knowledge of new medicinal chemistries arrived in number (along with American scientists returning from studies abroad), and fluctuating business cycles and sociopolitical conditions occasionally produced circumstances conducive to economic growth and development (the Civil War, for example, was an especially prosperous time for medicine makers). Some of the more successful drug firms located in urban centers took advantage of new opportunities presented to them by these happenings and social processes. They expanded and streamlined their operations and diversified and updated their product lines. The names of these companies are still familiar to health care consumers – there were, for example, Squibb in New York, Smith Kline in Philadelphia, Parke Davis in Detroit, Eli Lilly in Indianapolis, and Upjohn in Kalamazoo, Michigan. Philadelphia, New York, and points in between featured the greatest concentration of large manufacturers, and this area remains today the center of the American pharmaceutical universe. These mid and late nineteenth century developments in the drug industry were consequential in historical terms. They defined a basic template of organizational structure, growth, and geographic location that the industry would follow for the next century.

---

for example, Alfred D. Chandler, Strategy and Structure: Chapters in the History of the Industrial Enterprise, Cambridge, MA: MIT Press, 1962.

Still, Liebenau argues, economies of scale and advantages accruing to size and hierarchical divisions of labor did not become significant for the competitive structure of the industry until around the turn of the 20th century.[20] Investments in manufacturing allowed the biggest drug makers to grow ever larger, yet through the end of the 19th century, small producers, including makers of patent medicines, continued to thrive. Techniques of mass production afforded advantages in the manufacture and distribution of the controlled preparations that physicians tended to endorse and prescribe, but not necessarily in the promotion and sale of patent medicines.[21] Many Americans at the time shunned physicians and went directly to local apothecaries for medicines and advice; markets for patent medicines were preserved by the custom. In fact, public demand for these tonics was so robust that the large firms continued to prepare and market their own. Sizable portions of their profits were derived from sales of patent remedies and much of their advertising targeted pharmacies and consumers rather than physicians. The final transformation of the American pharmaceutical industry into a field of corporate giants in nearly complete control of drug distribution could not begin until the leading companies were able to distinguish their goods from those of the patent medicine vendors, and to eliminate this source of competition. This they did by forging institutional alliances with the medical profession and academic scientists – making themselves 'scientific'

---

[20] Liebenau, Medical Science and Medical Industry, ch. 1.

[21] Few of these potions were actually patented. More often, they bore trademarks protected by copyrights. The medicines themselves were dubbed proprietary not because ingredients, formulations, or processing techniques were published and original, but rather because they were secret. See Peter Temin, Taking Your Medicine: Drug Regulation in the United States, Cambridge, MA: Harvard University Press, 1980; chs. 1-2.

in the process – and by lobbying successfully for government regulation of drug manufacturing and marketing.

The medical profession was a natural ally of the large pharmaceutical houses. As historian of medicine Paul Starr reports, the American Medical Association was, from its inception in 1846, "at odds with the patent medicine business."[22] The doctors naturally took dim views of both self-medication and apothecaries who dispensed drugs and medical advice without professional credentials. Wherever these practices were common, Starr says, "[t]he nostrum makers were the nemesis of physicians. They mimicked, distorted, derided, and undercut the authority of the profession."[23] In response, the AMA made a show of distinguishing between medicines advertised exclusively to medical professionals and those sold directly to the public. The former it promoted as 'ethical' preparations; the latter it disparaged and discouraged (and in this, the AMA was supported by journalists' reports on the hazards associated with uses of many proprietary tonics). So, the commercial ends of the drug makers and the professional ends of the doctors came together in a common practical objective – discrediting the claims to quality, safety, and efficacy offered by makers of patent treatments and cures. Increasingly, the big drug makers attempted to enhance their reputations by marketing their products exclusively to medical doctors, and by borrowing the rhetoric of the physicians to advertise their formulations and practices as 'ethical,' too – i.e., reputable, trustworthy, consistent, and accountable in ways that patent medicines and their makers and vendors were not.

---

[22] Starr, The Social Transformation of American Medicine, p. 128.

[23] Starr, The Social Transformation of American Medicine, p. 127.

The basis of 'ethical' practices in the medical profession, according to spokespersons for the AMA, and of 'ethical substances' in the pharmaceutical business, according to the advertising campaigns of large drug manufacturers, was science. Reputable practitioners were accountable practitioners, and accountability in this context was afforded by the application of reliable scientific methods and rigorous scientific standards to drug manufacturing and physician-directed administration of therapeutic compounds. Fixing the imprimatur of 'science' on their goods and services allowed the doctors and the large drug companies to differentiate themselves from their competitors and to assume control (in a partnership of sorts) of pharmaceutical manufacturing and distribution. This strategy was made possible and effective by the considerable institutional and organizational development of the sciences over the course of the 19th century – a development that, in turn, reflected the growing cultural significance of science in American life. In this period, experimental inquiry became widely accepted as a superior way of understanding the phenomenal world in abstract, theoretical terms, and as a reliable source of useful practical knowledge as well. Places were furnished for experimental practices in American institutions of higher learning. Science was relocated from private residences to colleges, laboratories proliferated, and professors became directors of research.[24] For both doctors and drug makers, groups with professional and commercial interests in science, the emergence of the American university as a social institution and a home

[24] Roger L. Geiger, To Advance Knowledge: The Growth of American Research Universities, New York: Oxford University Press, 1986.

for scientific inquiry was consequential. By the second half of the 19th century, gaining access to scientific knowledge and resources meant going back to school.

According to Starr's history of American doctoring, the convergence of modern science and modern medicine began in this country with a broad movement to reform medical education. Initiated around 1870 with the reorganization of the Harvard Medical School, the movement was spearheaded by 'traditional' practitioners (dubbed 'allopaths' by professional rivals).[25] The ostensive goal of the reformers was to improve professional practice by imposing higher standards in training. Starr points out, however, that the stricter admissions requirements and greater curricular rigor also served definite interests in political battles for occupational control – those of the 'allopathic' orthodoxy against gangs of irregular practitioners, including homeopaths, osteopaths, chiropractors, herbalists, Christian Scientists, and midwives. Starr describes the reforms as elements of a concerted and self-conscious effort to produce greater homogeneity and cohesiveness within the profession – they were weapons raised by the AMA and the allopathic orthodoxy against their 'irregular' adversaries. New standards were imposed partly to facilitate the exclusion of marginal groups from bona fide professional membership. The mainstream reformers had decided that the way to greater powers, enhanced authority, and higher status for the profession led through the doors of science. The genuine professionals would become scientific and

---

[25] Paul Starr, The Social Transformation of American Medicine, pp. 113-115. 'Allopathy' refers to a mechanistic conception of health and illness and an interventionist approach to healing. It is still used to distinguish conventional, mainstream medicine from holistic alternatives. As an episode in the professionalization of medicine, the allopathic reform movement would eventually culminate in Abraham Flexner's 1910 report on the state of American medical education. Flexner's survey indicated that wide variations in standards and quality still existed across teaching institutions; the document served to justify a final weeding of the unscientific and the unorthodox from the professional ranks.

those who failed to do so would fall by the wayside. The orthodox doctors' efforts to impose this vision of professional practice were eventually successful, and the acquisition of medical credentials thereafter included the acquisition of scientific credentials. The association of medicine and academic science was consolidated as mainstream medical colleges, at the behest of the AMA and local and state professional associations, began purposefully aligning themselves with emerging research universities and their science faculties. Clinical research was established as a formal occupational specialty and the profession became 'rigorous' and 'scientific.' In its new university settings, as Starr relates, American medical education "became dominated by scientists and researchers and doctors came to be trained according to the values and standards of academic specialists."[26]

The reformers' turn to science as a means of reshaping the social character of medicine was adroit. This internal occupational transition was only part of the story. Becoming 'scientific' allowed the medical reformers to establish themselves as gatekeepers with the capacity to regulate, not only entry to the profession, but public access to medical goods and services as well. Science permitted the medical profession to enforce internal organizational discipline, but also to define the boundaries of its own jurisdiction, and to exercise greater influence and control in dealings with outsiders (patients, nurses, hospitals, government bodies, or drug makers, for example). Science enabled doctors to consolidate their cultural authority in matters of health and illness, enhance the social standing and rewards of the profession, and win the broad allegiance and trust of the American public. After the

---

[26] Starr, The Social Transformation of American Medicine, p. 123.

turn of the century, physicians rapidly established and expanded a professional monopoly.

Still, despite the fact that some important technical advances were introduced to medical practice and the pharmaceutical industry during this time, Liebenau and Starr assert that the rhetoric of science rather than new therapies or substantive improvements in the pharmacopoeia had the greater historical impact. Historians of science, industry, and medicine today examining this period in American history generally agree. They have concluded that the scientific approach to medicine and drug production discharged most of its special magic on the body social, and, specifically, in the area of institutional image-making, where it functioned as a tool for changing minds. In the case of medicine, Starr maintains that "science worked even greater changes on the imagination than it worked on the processes of disease."[27] Orthodox physicians secured scientific credentials in order to establish in the public consciousness the superiority of their information and healing practices vis-à-vis those of the 'irregulars,' and the superiority of the 'ethical' drugs that they prescribed vis-à-vis those hawked by the apothecaries and the patent medicine makers. These efforts to transform public opinion and habits were successful, but Starr suggests that the extent to which the doctors' methods and prescriptions were actually superior and the extent to which they were improved by the science of the day were perhaps exaggerated by many professional claimants.[28]

---

[27] Starr, The Social Transformation of American Medicine, p. 18.

[28] Starr, The Social Transformation of American Medicine, pp. 134-140.

To be sure, promoters of scientific medicine could point with pride to certain achievements. From the 1860s, bacteriologists had been shedding new light on the workings and pathologies of human beings and other organisms. In the process of articulating the germ theory of disease, Louis Pasteur and Robert Koch were able to identify numerous pathogenic bacilli, and they managed to develop vaccines against a few. Medical researchers following their examples were able to come up with several additional vaccines (against typhoid, cholera, and plague, for example) before the turn of the century. During the same period, early works in the fields that would become known as 'biochemistry' and 'clinical chemistry,' along with immunologists' serological investigations, were transforming and expanding modern understandings of the nature of health and illness in profound ways.[29] These studies also facilitated practical improvements in medicine. They were often pursued by medical researchers trained in chemistry, or by academic chemists in conjunction with medical clinicians, and often in laboratories affiliated with hospitals and medical schools.[30] The turn to

---

[29] On the influence of chemistry on medical practice during the early 20th century, historian Olga Amsterdamska says, in a monograph on Donald van Slyke, a key figure in the technical maturation of clinical laboratory methods: "it is not just that physiological or pathological states are redescribed in chemical terms, or that physiological phenomena are given a chemical interpretation, but rather that the chemical theoretical representation itself became autonomous, structuring classifications, ideas of disease, and the course of further research. Olga Amsterdamska, "Chemistry in the Clinic: The Research Career of Donald Dexter Van Slyke," pp. 47-82 in Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s, eds. Soraya de Chadarevian and Harmke Kamminga, Amsterdam, Netherlands: Harwood Academic Publishers, 1998; quote on p. 61.

[30] Formal institutional and informal personal interactions, associations, and accommodations among doctors, clinical technicians, and academic researchers – in the scientific commons of the clinical laboratory – continued to shape medicine and biomedical science through most of the twentieth century. See Johannes Büttner, History of Clinical Chemistry, Berlin: Walter de Gruyter, 1983; Soraya de Chadarevian, and Harmke Kamminga, eds., Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s, Amsterdam, Netherlands: Harwood Academic Publishers, 1998; Robert E. Kohler, From Medical Chemistry to Biochemistry: The Making of a Biomedical Discipline, Cambridge; Cambridge University Press, 1982; and Louis Rosenfeld, Origins of Clinical Chemistry: The Evolution of Protein Analysis, New York: Academic Press, 1982.

biochemistry revolutionized the art of diagnosis, through the invention of new tests designed to uncover reliable evidence of disease in samples of blood, urine, and other bodily fluids and tissues. These were major steps forward for biomedicine. Still, by the turn of the century, scientific progress had produced few therapeutic novelties. Much was being learned, but relatively little of it was being translated into information or chemical or biological agents that doctors could employ to treat their patients.

Medicine cabinets reserved for new scientific therapies would remain sparsely stocked for another two decades. Scientists had not yet significantly enhanced physicians' capacities to intervene when bodies became diseased.[31] At the turn of the 20th century, the epidemiological health and illness profiles of populations in developing countries began to improve considerably and rapidly, particularly in rates of morbidity and mortality associated with infectious diseases. These changes were dramatic and unprecedented, but the scientific advances of the day had only marginally enhanced physicians' capacities to rid bodies of harmful pathogens; these advances do not account for the epidemiological facts. That scientific medicine emerged in Europe and the U.S. just as rates of infectious disease began to decline appears to be mostly coincidental. Rather than crediting scientific medicine, historians explain the epidemiological evidence by pointing to better sanitation and effective public health initiatives: Western societies had cleaned up human environments and introduced healthier living conditions (at least insofar as infectious diseases were

[31] The parallels in terms of practical utility between the introduction of the germ theory of disease and the current advances in genetics are noteworthy. The hope that knowledge of the genome will be translated into effective treatments and cures for diseases is, as yet, mostly unrealized.

concerned). The sciences had taught developing societies how to arrest the transmission of infectious agents.

The rationales behind public health deterrents were rooted in new bioscientific knowledge, but the historians emphasize that the most important benefits of the germ theory of disease were realized in the prevention of disease, not in medical cures.[32] In medical practice, as Starr points out, antiseptic surgery probably did more to benefit patients than new drugs introduced at the time, and certainly no developments of the day exerted greater influences on practical doctoring than innovative advances in medical instrumentation (inventions or refinements of microscopes, stethoscopes opthalmoscopes, laryngoscopes, X-rays, spirometers, electrocardiographs, and so on) and the serologists' new chemical and bacteriological procedures for detecting pathogens and disease states.[33] With a handful of vaccines and antiserums standing as

---

[32] See, for example, John B. McKinlay and Sonja M. McKinlay, "The Questionable Contribution of Medical Measures to the Decline of Mortality in the United States," Health and Society 55, Summer 1977, pp.405-428. In response, Starr contends that the contributions of doctors (and scientific medicine) to public health have been unfairly disparaged. He notes that the McKinlays neglected the introduction of diptheria antitoxin and failed to acknowledge adequately the contributions that medical practitioners made to programs and agencies organized to monitor or improve living conditions and their effects on health: "By providing more accurate diagnosis, identifying the sources of infection and their modes of transmission, and diffusing knowledge of personal hygiene, medicine entered directly into the improved effectiveness of public health." Starr, The Social Transformation of American Medicine, p. 138.

[33] Starr, The Social Transformation of American Medicine. As laboratory testing became an important component of medical practice, manufacturers of medical instruments began to cater to the technical wants and needs of clinical chemists. Clinical chemists analyze bodily fluids and tissues of various kinds in vitro in order to infer states of health or disease in vivo. In the late 19th century and early 20th century, a large market emerged for the equipment, supplies, reagents, and so on, that clinical laboratories required to do their diagnostic work. In the U.S., as in Europe, companies were formed or refocused in order to meet the demand. As testing protocols multiplied and became more sophisticated and specialized, a few industry leaders grew to dominate national markets – Evan Kimble's glassware operation and Arnold Beckman's instrument business, for example. The formation of the diagnostics industry laid important institutional groundwork for the emergence of the biotech industry in San Diego. Although by the time of its IPO, Hybritech was advertising itself as a pharmaceutical company, the firm's profits were derived from the sale of radioimmunoassay kits – quantitative diagnostic tests that employ antigens and antibodies as reagents, and measure interactions between the two as the basis

notable exceptions to the general rule, the scientific approach to medicine did not immediately generate effective therapies or cures for diseases. Yet, scientific medicine was remarkably successful in social and institutional terms. The special cultural authority that became attached to scientific knowledge in the latter half of the 19th century radically transformed the ways in which emerging modern societies organized the management of bodily health and illness in individuals and various social groups. Increasingly, doctors assumed responsibilities in this sphere of social life, despite the fact that, insofar as healing was concerned, their technical capabilities had not advanced significantly.

RATIONALIZING DRUG PRODUCTION

These changes had a major impact on the development of the drug trade. Liebenau and Starr both describe how the doctors not only vanquished rivals within medicine; their social elevation came at the expense of proprietary tonics and their makers and marketers as well.[34] With science on their side, the physicians were able to refute categorically advertising claims that touted the benefits of patent elixirs. As more sick people placed their faith in scientific medicine, they turned to doctors rather than apothecaries for medical information and treatments, and physicians assumed far

---

for clinical inferences. By the late 1970s, radioimmunoassay was a standard laboratory test format. Several major diagnostics manufacturers sold radioimmunoassay products. Hybritech improved tests for a number of different antigens by incorporating monoclonal antibodies. In addition, Hybritech recruited key personnel from leading competitors in the field, including Abbott, Technicon, the Hyland division of Baxter Travenol, and the Ortho division of Johnson & Johnson. On the development of radioimmunoassay in the 1950s and 1960s, see Louis Rosenfeld, Origins of Clinical Chemistry: The Evolution of Protein Analysis, New York: Academic Press, 1982. On the formation and evolution of the diagnostics industry, see Louis Rosenfeld, Four Centuries of Clinical Chemistry, Amsterdam, Netherlands: Gordon & Breach Science, 1999.

[34] Liebenau, Medical Science and Medical Industry, ch. 2; Starr, The Social Transformation of American Medicine, pp. 127-134.

greater influence and control over the use of drugs. In these circumstances, pharmaceutical manufacturers became increasingly dependent on doctors as customers, and increasingly sensitive and responsive to the demands of this particular group of buyers. And what the doctors wanted in pharmaceutical products, above all, were composition standards that would permit more informed decisions about what to prescribe and how much. They sought consistency in formulations, greater precision in dosing, and, they expected to see, as a result, generally improved outcomes for patients.

Liebenau's history of the American pharmaceutical industry chronicles the natural response of drug makers – those with sufficient capital to overhaul and retool their operations – as they sought to make themselves scientific, too.[35] Closer associations with medical science became key features of large pharmaceutical manufacturers' business strategies. Becoming scientific, the big firms judged, would help them to achieve commercial goals. It would enable them to distinguish themselves from competitors and to capture larger shares of the national markets that were being created at the time by the creeping standardization of medical practice. So, the major companies attempted, some with success, to cultivate extensive and exclusive relationships with doctors and professional medical associations, and they worked to supply products that the new scientific medicine men would endorse and prescribe. One effective means of exploiting national markets, they found, was to recruit massive armies of salesmen to distribute standardized products to physicians

[35] Liebenau, Medical Science and Medical Industry, ch. 3.

hither and yon, all the while emphasizing the 'ethical' character of their business and the scientific character of their compositions. They also learned that, in addition to introducing machines and the organizational technologies of mass production to their operations, the best available means of ensuring the quality of medicinal preparations in terms of consistency, purity, safety, and efficacy, and maintaining that quality in high volume batches, was to apply scientific methods of analysis in drug formulation and manufacturing processes.

These changes began to occur on a broad scale in the 1890s, a decade that Liebenau calls "watershed years" for the American pharmaceutical industry. He observes that, by this time, "many of the leading companies were projecting a new and avowedly scientific image: they began to employ medical men and maintain laboratories for quality control, standardisation, and, in some cases, product development."[36] The turn to science had a major impact on the competitive structure of the pharmaceutical industry because it introduced new economies of scale that favored higher volumes of production. The victory of the scientific approach in medicine transformed the pharmaceutical marketplace. It created a swelling demand for standardized ethical drugs that could be met only by introducing 'scientific' means of production. As these drugs colonized and came to dominate more markets, per unit costs of production plummeted for firms that could afford to employ the latest technologies and manufacture in very large quantities.

---

[36] Liebenau, Medical Science and Medical Industry, pp. 4-5.

Organizational survival rates in the industry began to reflect these new trends. The drug companies that could position themselves to challenge rivals and exploit emerging markets were those possessed of the technical know-how and the material resources necessary to manufacture and ship scientific products in high volume batches. Profits diminished for the rest, and smaller firms began to disappear. Around 1890, prevailing winds in the American pharmaceutical business converged to produce an eddy in which science and organizational size, together and synergistically, bestowed competitive advantages.[37] The new 'evolutionary principle' that appeared to govern organizational fates in this environment (i.e., 'survival of the big and scientific') redefined the field and would continue to determine, from a macroscopic perspective, at any rate, the broad contours of competition in the drug trade for the next century.

Liebenau argues that the rhetoric of science also played an important role in the evolution of the American pharmaceutical business. The waves of corporate consolidation that swept through the field in the early decades of the 20th century followed the transfer of scientific practices to medicine, along with resultant shifts in relations between medical professionals and their patients and the character of markets for medicinal products. Following the lead of the medical profession, and in response to the demands of the doctors as pharmaceutical consumers, America's big drug manufacturers likewise began to establish connections, toward the end of the 19th century, with institutions of scientific research. They did so in order to improve the intrinsic quality of the goods and services that they offered, certainly, but also to

---

[37] Liebenau, Medical Science and Medical Industry, ch. 3.

establish the legitimacy of their practices and products in environments in which scientific criteria had become gold standards. Like physicians, they were seeking to enhance and upgrade their public images and to distance themselves from competitors in the process. The drug makers began to import scientific practices and recruit scientific personnel from research universities, and they revised their internal standards, methods, and operational routines in ways that reflected scientific values. Their objective was to be able to promote their commodities as genuinely 'scientific.' Pharmaceutical marketers could advertise their preparations as safe, reliable, and efficacious if they were formulated and packaged according to scientific guidelines. Because they supplied markets dominated by scientific medicine men, it behooved producers to adopt scientific criteria as industry benchmarks.[38]

However, just as scientific advances of the day did not immediately boost the healing powers of the medical profession, neither did investments in science immediately yield product innovations for pharmaceutical firms. In most instances, there were no expectations that they would; few drug companies intended to institute or expand research and development programs. They did not envision themselves moving into the business of making science-based innovations.[39] These firms devoted very little time or money to the discovery of new cures, new knowledge of the body and processes of disease, or new information about the pharmacological properties of

---

[38] Liebenau, Medical Science and Medical Industry, ch. 9.

[39] The leading exceptions were the H.K. Mulford Co. in Philadelphia and Parke-Davis in Detroit. Their research operations, however, were modest in scale and narrow in scope. See Liebenau, Medical Science and Medical Industry; and John P. Swann, Academic Scientists and the Pharmaceutical Industry.

chemical compounds. The research and development projects that led to new drugs generally took place elsewhere. (In the U.S., at least, pharmacological research was undertaken mainly at universities, but in the decades surrounding the turn of the 20th century, biology and pharmacy science were both advancing farther and faster in Europe than in America, in both academic and industrial settings).[40] In the 1890s, American pharmaceutical manufacturers began to construct laboratories on their premises, but, with a few scattered exceptions, these facilities were used for quality control rather than product development.[41] Pharmaceutical scientists were typically engaged in testing the purity and consistency of drug formulations, and in small scale clinical testing of the safety and efficacy of medicines (work that was usually undertaken in collaboration with physicians).

Through the end of the century, medicinal preparations sold in the U.S. were as likely to be based on folk knowledge and traditional practice as on empirical evidence and theoretical explanations derived from systematic laboratory experimentation. Claims that pharmaceuticals were 'scientific' did not necessarily mean that there were chemical or biological explanations available to account for their therapeutic or analgesic properties. Instead, such statements indicated that their ingredients and compositions had been verified by chemical analysis. And in those cases in which drug formulas were patent-protected intellectual properties supported by published scientific research, i.e., 'verified' demonstrations of utility that specified functional novelties, the unique and original applications that justified the patent award, they

[40] Swann, Academic Scientists and the Pharmaceutical Industry, ch. 1.

[41] Liebenau, Medical Science and Medical Industry, ch. 9.

were not often controlled by American manufacturers. Usually, rights to manufacture were licensed to producers in this country by individual inventors or foreign holders. Industry historian John P. Swann reports that American drug companies did not make extensive use of the patent system in the first two decades of the 20th century, and that, until World War I, German firms held most U.S. patents on therapeutic agents.[42] American pharmaceutical companies simply did not employ scientific experimentation as a tool of drug discovery.

Still, in order to cloak themselves in the legitimacy of science, American pharmaceutical houses, just like the doctors, were obliged to knock on the doors of the country's colleges and universities. The evolution of the modern pharmaceutical industry in the late 19th and early 20th centuries was, for this reason, still closely linked to the rise of scientific medicine, and like scientific medicine itself, to the intensification of basic scientific inquiry that was taking place in a new American institution, the research university. However, the researchers with whom the pharmaceutical companies initially established connections were not usually biomedical scientists. The academic funds expertise that interested commercial drug makers were found in schools of pharmacy and departments of chemistry, where they had been accumulating fitfully over the second half of the 19th century. The development of pharmacological chemistry as an academic specialty arguably had more impact on drug production in the U.S. than that of any other scientific field.

By the 1890s, the biological sciences were able to make some important contributions to commercial drug-making. These years saw the first significant

---

[42] Swann, Academic Scientists and the Pharmaceutical Industry, p. 31.

therapeutic breakthroughs to be delivered by scientific medicine – new biological drugs discovered in European laboratories. Diptheria antitoxin was the first and a number of other therapeutics and vaccines followed. These discoveries became important scientific milestones for the U.S. drug trade – several companies were prompted to start making and marketing biologics. In order to do so, they found it necessary to establish some ties with university-based bacteriologists who had learned how to manufacture and handle these substances. American drug firms thus began to incorporate established bioscientific knowledge and expertise into their operations, and, in a few instances, these investments encouraged some initial forays into private biological research. Manipulations of biological processes have also played important roles in the pharmaceutical manufacturing since the industry began to take its now familiar form in the 1930s. Mass aerobic fermentation, for example, is still the standard means of extracting antibiotic compounds, vaccines, and vitamins from mold, fungi, bacteria, and other microorganisms. But the theoretical foundations of microbiology as they apply to techniques of industrial bioprocessing have remained more or less static over this period. The task of making incremental improvements in the field of applied microbiology was abandoned long ago by biologists, for the most part. Tinkering with conventional approaches to industrial bioprocessing has been, for many years, the province of chemical engineers.[43] Throughout much of the 20th century, academic research in the life sciences and the industrial design and production of drugs and other medicinal substances proceeded on largely independent paths.

---

[43] Pauline M. Doran, Bioprocess Engineering Principles, San Diego, CA: Academic Press, 1995.

The staple scientific techniques employed in American pharmaceutical labs have been borrowed, in the main, from academic pharmacists and analytical chemists, and not biologists. After the turn of the 20th century, chemists began moving from laboratories in institutions of higher learning to commercial laboratories. As they transferred their specialized practices in the process, significant internal changes in drug manufacturing resulted. The methods and standards employed in the preparation and testing of medicinal products became 'scientific.' However, while these trends led to the designation of certain drugs as 'ethical,' and so, presumably, superior in quality to 'patent medicines,' they did not result in the invention of new pharmaceutical agents. Not until the 1930s would events prompt American drug companies to develop genuinely innovative research and development programs.

The large drug companies also began to lobby for federal regulation of the industry during the 1890s. This, too, was part of the industry's turn toward science – they wanted regulation based on 'scientific principles,' and not politics. The big firms welcomed and encouraged federal watchdogs because regulation promised to thwart their competition, the pesky sellers of patent medicines. For their part, reform-minded politicians at the height of the Progressive era were intent on legislation that would protect consumers, and commonplace reports of useless or poisonous patent medicines had attracted their attention. The progressive reformers were perhaps less than enthused about the odd match they were making with big business when it came to drugs, but they recognized that small producers represented the greater threats to the public at the time, in terms of both physical and monetary injury. They wanted to

ensure drug safety and to combat fraudulent claims and practices, and they saw that making the drug trade scientific was a way of holding it accountable.[44]

In 1902, after sales of tainted vaccines caused well-publicized injuries and deaths in Camden, New Jersey and Saint Louis, Missouri, Congress quickly ratified new rules to prevent such tragedies – the Biologics Act. The act mandated inspections of manufacturing facilities by the Public Health Service and the government's Hygiene Laboratory, and required producers of biological substances to be licensed by the Department of the Treasury. Consequently, only firms that could afford to modernize production facilities, maintain scientific staffs, and demonstrate compliance with the regulators' standards for product purity remained viable competitors in the market for serums and vaccines. This law was followed, in 1906, by the passage of the original Pure Food and Drugs Act. The 1906 Act targeted mislabeling, adulteration, and fraudulent representations of composition and purity. It required that ingredients be listed accurately on product labels. The Department of Agriculture's Bureau of Chemistry was empowered to analyze samples and to initiate legal action against violators. Penalties included confiscations, fines, and shut-downs. The 1906 Act applied broadly to all products touted as medicinal, not just to biologics. Sales of patent medicines (i.e., those containing 'secret ingredients') began to flag in short

---

[44] For scholarly works on drug regulation and the history of the FDA, see Henry G. Grabowski, Drug Regulation and Innovation: Empirical Evidence and Policy Options, Washington, D.C.: American Enterprise Institute for Policy Research, 1976; Charles O. Jackson, Food and Drug Legislation in the New Deal, Princeton, NJ: Princeton University Press, 1970; Jonathan S. Kahan, "The Evolution of FDA Regulation of New Medical Device Technology and Product Applications," Food , Drug, Cosmetic Law Journal, 1986, 41: 207-214; Peter Temin, Taking Your Medicine: Drug Regulation in the United States, Cambridge, MA: Harvard University Press, 1980; James Harvey Young, ed., The Early Years of Federal Food and Drug Control, Madison, WI: American Institute of the History of Pharmacy, American Pharmaceutical Association, 1982.

order, while costs of doing business for those concocting the potions were magnified. Overnight, the abilities of patent medicine vendors to compete with large firms vanished nearly completely. They typically lacked the financial and scientific wherewithal necessary to ensure compliance.

The technical consequences of the legislation were greater quality control and the gradual standardization of medicinal products. The social, economic, and organizational changes encouraged by the new laws included the disappearance of strictly local markets and rapid consolidation among pharmaceutical houses. With the advent of regulation came a new kind of competitive environment. Economies of scale became operative in the industry. There were many subsequent mergers and acquisitions in the field as the industry reorganized. New alliances were forged among the survivors. They recognized common political interests and came together, in the midst of fierce competition, to pursue them in Washington and in statehouses around the country. National and regional trade associations were established. Among them was the Pharmaceutical Research and Manufacturers of America (PhRMA), which eventually became the largest and most powerful of these organizations. The new laws also represented formal governmental approval and endorsement of science in the manufacture of drugs. In effect, this stood as support for and complicity with the economic forces that were working on the industry. Producers were compelled by regulators to make their operations 'scientific,' and to grow at accelerating rates. As they expanded and attempted to function more efficiently they not only developed techniques of mass production, they also built laboratories, hired scientific personnel, and incorporated the latest scientific tools and

methods into their operations.[45] Government regulation in pharmaceuticals represented an institutional, cultural, and ideological victory for 'science.'

Yet, innovative product development based on scientific techniques was still not a component of American firms' routines or plans. It would take some time and some external shocks to the industry before American pharmaceutical houses would find it necessary or desirable to establish their own in-house R&D programs. World War I was especially important in this regard because it interrupted trade with Germany and threatened the availability of important drugs in American markets. For decades, German firms had led the way in the discovery of new medicines. With supplies from these sources cut off or made significantly more difficult and expensive to maintain, American distributors were moved to begin developing their own R&D facilities. More chemists were added to company payrolls and equipped with new laboratories for the 'reengineering' of medicinal compounds discovered and refined by German scientists. Congress assisted by allowing special suspension of U.S. patent rights held by German firms, and providing tax and tariff relief for domestic drug producers. Eventually, American industrial scientists acquired the technical

---

[45] To summarize 20th century trends in American pharmaceutical production, I have relied on several economic analyses of the evolution and structure of the industry, including those by William S. Comanor, "The Political Economy of the Pharmaceutical Industry," Journal of Economic Literature, 1986, 24: 1178-1217; William S. Comanor and Stuart O. Schweitzer, "Pharmaceuticals," in The Structure of American Industry, 9th ed., Walter Adams and James W. Brock, eds., Englewood Cliffs, NJ: Prentice-Hall, 1995; Alfonso Gambardella, Science and Innovation: The U.S. Pharmaceutical Industry in the 1980s, Cambridge: Cambridge University Press, 1995; Henry G. Grabowksi, Drug Regulation and Innovation: Empirical Evidence and Policy Options, Washington, D.C.: American Enterprise Institute for Policy Research, 1976; U.S. Congress, Office of Technology Assessment, Pharmaceutical R&D: Costs, Risks, and Rewards, OTA-H-522, Washington, D.C.: U.S. Government Printing Office, February 1993; David Schwartzman, Innovation in the Pharmaceutical Industry, Baltimore: Johns Hopkins University Press, 1976; Meir Statman, Competition in the Pharmaceutical Industry: The Declining Profitability of Drug Innovation, Washington, D.C.: American Enterprise Institute for Public Policy Research, 1983.

sophistication of their German counterparts and successfully duplicated the synthesis of many pharmacological compounds.[46] With their new technical capacities, the American firms were prepared to embark on original research and development projects as well. They started to acquire and create intellectual properties for use as competitive tools, and they started patenting in order to protect them. The war effectively ended German dominance in pharmaceuticals. American drug makers subsequently incorporated processes of scientific innovation into their operations.

Research and development in American pharmaceutical laboratories expanded and became significantly more productive after the 1932 discovery (made by Gerhard Domagk, a German medical scientist) that sulfanilamide, a red dye, exhibited antibiotic properties. Laboratories around the world began searching for new sulfa drugs. More than six thousand different forms were synthesized and tested.[47] Through the 1930s, in both Europe and America, massive investments in research on antibiotics reinforced the status of random screening and synthetic refinement of chemical compounds as the principal technical bases of industrial drug discovery.[48]

---

[46] This was no simple undertaking because American chemists lacked the tacit knowledge and skills cultivated and guarded by the Germans. Using as an example the efforts of American researcher George W. Raisziss to synthesize Salvarsan, an anti-syphilitic compound, at the University of Pennsylvania, Liebenau explains: "At the outset the difficulty of this task was not appreciated because it was assumed that the patent Paul Erlich had taken out in the United States in 1910 would provide sufficient information to synthesize the drug. In fact, the complexity of the laboratory procedure, and the need for know-how possessed only by Erlich and his collaborators, at first thwarted Raiziss. After several months of frustrating attempts, however, his efforts eventually yielded the yellow powder." See Liebenau, Medical Science and Medical Industry, pp. 114-115. For sociological commentary on the ubiquity of tacit know-how in scientific work, see H.M. Collins, Changing Order: Replication and Induction in Scientific Practice, Chicago: University of Chicago Press, 1985.

[47] Lisa Ruby Basara and Michael Montagne, Searching for Magic Bullets: Orphan Drugs, Consumer Activism, and Pharmaceutical Development, New York: Pharmaceutical Products Press, 1994; p. 14.

[48] The development of methods for synthesizing vitamins provided a similar stimulus for R&D in the 1930s.

At the same time, massive returns in the form of revenues from antibiotic sales reinforced commitments of American firms to laboratory research. The fundamental methods employed to develop antibiotics and the magnitude of the returns on investment delivered by these drugs would characterize pharmaceutical R&D and the drug business for decades. The finishing touches on the structuring of the industry and drug science awaited the occurrence of one additional series of events in the 1930s, an extended episode that led, one author asserts, to the "the birth of the modern pharmaceutical trade."[49]

THE UNINTENDED CONSEQUENCES OF REGULATION

In 1937, a batch of sulfanimide contaminated with diethylene glycol, a poisonous solvent, was released by the Massengill Co. of Bristol, Tennessee. One hundred and seven people died, including many children. A public clamor arose for rules to prevent future catastrophes of this kind. The 1902 Biologics Act and the 1906 Food and Drugs Act had never been consistently enforced, and now they were widely judged inadequate, by the public, by politicians, and, often, by industry, as well. Although many worthless and potentially harmful products were kept off the market following the early legislation, the 1902 and 1906 acts arguably did more to alter the competitive environment of the pharmaceutical business than to protect consumers. They provided for after-market spot checks of medicines and investigations of claims of harm, but excepting the production of biological serums, did not require facility inspections or pre-market testing. In addition, for the three decades that had passed

---

[49] Philip J. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation, New York: Knopf, 2003; ch. 6.

since the introduction of these acts, the federal regulatory agencies responsible for pharmaceutical oversight had remained underfunded, understaffed, and poorly coordinated. The duties of their personnel were spread across several industries – agriculture, food production, and cosmetics, for example, as well as drugs – and often the activities of manufacturers within one or another were neglected for extended periods.

The FDA was not established as a separate law enforcement agency under the umbrella of the Department of Agriculture until 1927 (as the Food, Drug, and Insecticide Administration).[50] When it came, the move consolidated administrative functions, but did not solve budget shortfalls or alleviate burdens placed on over-worked field representatives. And, of course, the agency was subject to the influence of changing political regimes, as it remains today. In the relatively conservative, laissez-faire atmosphere of the 1920s, political support for tighter regulations or more effective enforcement was unavailable. In the New Deal era, however, the circumstances were quite different. Discussions of reforms to the original Pure Food and Drugs Act of 1906 were initiated on the floors of both Congressional houses in 1933. After five years of heated debate, and after the Massengill incident, which deposited the full weight of public opinion and powerful lobbies like the American Medical Association behind the reform movement, the Food, Drug, and Cosmetic Act of 1938 was passed and signed into law by President Roosevelt.

---

[50] Renamed the Food and Drug Administration in 1930, its bureaucratic residence was shifted to the Federal Security Agency in 1940. In 1953, the Federal Security Agency was renamed the Department of Health, Education, and Welfare (HEW).

The pharmaceutical companies were now ordered to determine and document the safety of their products before marketing them, and the FDA was designated as the agency to evaluate the evidence, and prohibit distribution if necessary. The intense scrutiny focused thereafter on medicinal products by the newly empowered agency was unprecedented. In addition, the purview of FDA regulations binding the drug companies was extended beyond product to process – the determination of safety now included the regular inspection and validation of manufacturing operations. No other market and no other group of commercial producers had ever been subject to this degree of governmental oversight. In order to respond to the new directives, the pharmaceutical companies again had to expand their laboratories, scientific activities, and rosters of scientific personnel, both in size and in scope. They hired many more toxicologists, pharmacologists, and chemical engineers who were set to the tasks of ensuring compliance. Soon after the 1938 Act was signed into law, the 'scientization' of the American pharmaceutical industry moved to completion.

Adapting to the new regulatory scheme was costly for the drug companies, but there were collateral benefits to be realized as well. The commitment to scientific practices and the hiring of additional scientific staff enhanced the technical capacities and capabilities of the drug companies in general terms. The 1938 Act coincided with, and served to encourage and speed, firms' decisions to move ahead with innovative R&D programs. Further, the additional demands for drug safety introduced a new logic of product development, one that emphasized quality rather than economy in pricing. If firms were required to guarantee the safety of their products and to lay out the additional costs of production, they would trade on the greater value of the

medicine. Not only would they charge more for their drugs, they would also advertise the improvements, and collectively rework the public image of the industry. Special scientific medicines derived from the application of special scientific methods and meeting special scientific standards were special kinds of commodities, or, at least, they could be marketed as such.

The 1938 Act laid the groundwork for the distinction between prescription and non-prescription drugs, classifications that were formally established by the Humphrey-Durham amendments of 1951. After the FDA demanded drugs of demonstratively higher value, manufacturers started competing with each other principally on the basis of quality. This, coupled with the race for new antibiotics and the concentration of chemical and pharmacological expertise in commercial settings, helped to spur innovation in industrial drug laboratories in the 1940s and 1950s. A marvelously successful system was created in this way, despite the steep costs and heavy regulatory burdens that characterized it. The number of effective drugs available to physicians multiplied rapidly during this period, as the engines of discovery and development became heated. The profit margins of the big drug companies multiplied rapidly, too. The drug companies that had managed to become scientific squeezed out smaller competitors early on. These organizations continue to dominate the field (for the present) and have grown into massive national and international corporations.[51] The business was transformed by pharmaceutical science and regulatory science into a battlefield of oligopolistic competition.

---

[51] And, in the current wave of mergers and acquisitions in the industry, some are still getting bigger, although the drivers of consolidation have changed. Journalist Milt Freudenheim calls recent corporate fusions "discover or die" mergers. See Milt Freudenheim, "Pharmacia Decides on Safe Course in

The long turn to science in drug manufacturing that began in the 19th century, and led, eventually, to the formation of the modern system, was not merely technical in character. It was also rhetorical. It generated social and political enthusiasm and support, and it had far-reaching organizational and economic consequences. In the new, rationalized industry that thrived on the development of innovative products, the capital investments required to scale up for mass production were enormous, the costs of organizing and administering large disciplined marketing and sales departments were enormous, and the monies required to conform manufacturing practices and pharmaceutical products to standards and rules enforced by government regulatory agencies were enormous, too. When outlays of this magnitude became competitive and operational necessities for significant industry players, the field was virtually barred to potential new entrants.[52] As pharmaceutical production became more 'scientific,' opportunities for starting new companies started to disappear. Being first on the scene provided the big 19th century drug manufacturers with competitive advantages that they never relinquished. Minor producers failed, assets were redistributed through mergers and acquisitions, the number of companies in the field

---

Market That Loves Robust Growth," New York Times, July 15, 2002. In the 'Big Pharma' sector of the drug trade, growth has not lately followed innovation so much as vacuums formed in its absence.

[52] The only additions to the roster of drug wholesalers in the first half of the 20th century were big chemical companies like Merck and Pfizer that had been supplying pill makers for many decades. In the 1930s, when the big drug companies began producing their own ingredients in bulk, Merck and Pfizer elected to begin making and marketing their own pills. See Meir Statman, Competition in Pharmaceutical Industy: The Declining Profitability of Drug Innovation, Washington, D.C.: American Enterprise Institute for Public Policy Research; p. 5. Thereafter, only one new player managed to find a spot in the field – Syntex, a small Mexican chemical company that first achieved success by pioneering the synthesis of steroids on an industrial scale. The company moved to Palo Alto, California and joined the ranks of the pharmaceutical elite in the 1960s when it developed norethindrone, the world's first oral contraceptive.

dwindled, domination of markets by the major players discouraged and thwarted newcomers, and eventually the U.S. pharmaceutical industry became populated by a relatively small number of huge and extremely profitable corporations.

A DEARTH OF INNOVATION

One additional struggle between corporate interests and liberal politicians in the early 1960s would finish setting the industrial stage onto which biotechnologists and bioentrepreneurs would first step in the next decade. Attempts at pharmaceutical innovation in the 1940s and 1950s were remarkably successful. Drug companies and their shareholders were rewarded handsomely. But some observers became troubled that huge profits were being reaped from products designed to improve human health, suspicious about the oligopolistic aspects of the system that generated these gains, and fearful of the wealth and power that were accumulating with the giant corporations in the field (and mostly in the mid-Atlantic states of Delaware, Pennsylvania, New Jersey, and New York). In Washington, Estes Kefauver, Democratic senator, and chairman of the Senate Subcommittee on Antitrust and Monopoly, was among them. After completing investigations of the steel and automobile industries, he decided, in 1959, to initiate hearings on the pharmaceutical trade.[53] When witnesses testified that pharmaceutical firms were not only producing therapies and vaccines that benefited consumer health despite their high costs, but were also sometimes successfully promoting, selling, and recouping R&D expenditures on clinical failures that did no harm, Kefauver introduced to the Senate (as did Democratic congressman Oren Harris

[53] For a detailed account of the political machinations surrounding the Kefauver hearings, see Philip J. Hilts, Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation, New York: Knopf, 2003; chs. 9-11.

of Arkansas to the House of Representatives) a bill to amend the Food, Drug, and Cosmetic Act of 1938.

The legislation called for pharmaceutical companies to demonstrate the efficacy of new drugs, as well as safety, prior to marketing. It was fiercely contested by the industry and its conservative political allies, but passed in 1962 with assistance from the thalidomide scare. The bill's new rules for clinical trials poked at the FDA for the industry-friendly approach it had adopted during the 1940s and 1950s, and for several safety failures that had occurred on its watch. It included provisions for more stringent safety testing (additional and better tests and data), inclusions that, following the showcasing of thalidomide horrors in the media, made opposition far more difficult for members of Congress to defend publicly. The Kefauver-Harris amendments significantly strengthened the FDA. Previously, under the 1938 Act, rights to market were automatic unless regulators discovered reasons to halt distribution within sixty days of a new product filing. That principle was turned on its head in the 1962 Act. Pharmaceutical companies now had to plead for approval and could not move without explicit permission from the government. Unlike the 1906 and 1938 Acts, the Kefauver-Harris amendments did not alter the basic competitive structure of the pharmaceutical industry, but implementation of the new rules produced nearly immediate effects. After the 1962 regulatory changes, rates of pharmaceutical innovation went into a tailspin. Between 1950 and 1962, new drug

introductions averaged fifty-six per year. From 1963 to 1975, after FDA approval of both safety and efficacy testing was required, the figure was reduced to seventeen.[54]

Economists and historians have long argued over how best to account for this steep decline in R&D productivity. Four main explanations (that are not mutually exclusive) have been advanced. First, it has been suggested that clinical testing procedures conducted with greater rigor according to the new rules may have weeded out a significant number of ineffective candidate drugs, just as the Kefauver-Harris legislation intended. The FDA and its supporters have naturally favored interpretations of this kind. A second, and very different account, holds that after the new law took effect, drug companies were required to spend considerably more on each compound that they chose to continue investigating into clinical stages. As development times mounted and testing expenses increased, fewer resources were left available to fund research on alternatives. Consequently, development pipelines began, not only to slow, but to clear out and empty. Opponents of the legislation maintained that the public would not be served, but instead would ultimately suffer. Industry partisans situated in many different institutional quarters have been making arguments along this line ever since Kefauver began his challenges. They still complain perennially about regulatory constraints that they see as redundant or unnecessary. It is a debate without an end – it is built into the structure of the system, so to speak – and voices in biotechnology have now joined the chorus.

A third story suggests that the lag of innovations may have been caused, in part at least, by delays at the FDA. Until recent calls from the public and their

---

[54] Grabowski, Drug Regulation and Innovation, p. 18.

representatives in government for expedited approvals of drugs designed to treat dread and often fatal diseases like AIDS and certain kinds of cancer, FDA personnel had few incentives to speed review processes. Protecting consumers in the marketplace has always been a greater part of the agency's mission than ensuring or improving the quality of medical care. Since 1962, at least, the FDA has been predisposed to err on the side of caution, and to move deliberately. In addition, although the Kefauver-Harris amendments significantly increased the amount of work to be done by the FDA, the agency remained under-funded and under-staffed. The reduction in new product approvals almost certainly reflected, in part, the inability of regulators to keep up, to manage effectively the increased complexity of the testing process, the greater flows of scientific data arriving in the mail, and the re-education of pharmaceutical scientists and executives. These problems may have combined to slow the entire development process from start to finish. Parties on both sides of the political fence bring this point up, some to support more agency funding, others to discourage it or promote streamlining efforts.

Lastly, in a condition not directly related to the regulatory environment, the discovery procedures of the industry started to falter at about the time of the Kefauver hearings. The traditional 'empirical' method of drug discovery begins with the random screening of compounds for pharmacological activity. The aim is to identify those that interact with molecular disease targets. When activity is detected, the techniques of organic chemistry are applied to characterize the active molecules, to synthesize variants with desired properties, and to begin the long process of testing candidates to find which might actually be useful as drugs delivered in vivo. In the

1960s, this method began to show signs of decrepitude as a tool of drug development. Drug company chemists found themselves having to roam further afield in search of promising compounds. It appeared that unless they lucked into new classes of therapeutic agents or invented new techniques that would permit finer resolutions in the characterization and manipulation of small molecules, pharmaceutical companies would have to learn to live with high degrees of uncertainty regarding returns on R&D spending. In a 1974 speech, FDA Commissioner Alexander Schmidt cited the technological and conceptual fatigue of medicinal chemistry as the reason why new product innovation was flagging in pharmaceuticals (perhaps partly to deflect blame cast on his agency):

> ...in many areas of biomedical knowledge, we are on a plateau. We have temporarily exhausted the exploitation of known concepts and tools. Truly dramatic new progress in medicine now waits on some basic innovation in molecular science, some breakthrough in our understanding of disease mechanisms, some new therapeutic concept or tool.[55]

The post-1962 pharmaceutical industry described by Schmidt was the destination of biotechnologists and biotechnologies when they first left their academic homes. In technological terms, it seemed to be winding slowly down into stagnation. The pharmaceutical business was science-based, but the main science was chemistry. Industrial labs conducted clinical toxicological and pharmacological studies, but biological investigations into processes of disease were not yet included in industrial research programs. These remained housed at universities and institutions of basic

---

[55] Quoted in Grabowski, Drug Regulation and Innovation, p. 19. Schmidt was apparently unaware of Boyer and Cohen's invention of recombinant DNA techniques the previous year, or, at least, the potential applications of rDNA in medicine. He did, however, identify biochemistry and molecular biology as the disciplines of the future in an industry waiting for something to happen.

scientific research.[56] As the character of pharmaceutical science and the structure of the pharmaceutical industry took shape together in the latter half of the 19th century and the first half of the 20th, this social boundary became well-established and well-defined. By the 1970s, a dearth of innovation had come to characterize one side of the line, while an explosion of creative research was ready to be released on the other.

As an organizational field, the pharmaceutical business had become an oligopoly in which giant corporations squared off against each other in fights for market share. A staggering amount of resources had to be marshaled in order to compete. Further, the size and strength of the regulatory apparatus overseeing competition in the field (ostensibly in order to protect the by-standing public) was unparalleled, especially after the Kefauver-Harris legislation. The demanding standards imposed by the regulators on industry participants added substantially to the price of admission. Only the fattest cowboys with fifty-gallon hats and bankbooks the size of Dallas could afford the financial and scientific stakes. Breaking in by conventional technological and organizational means seemed a virtual impossibility. The post-1962 pharmaceutical industry was ripe for technological innovations, but these would not be realized until accompanied by effective social and organizational innovations. By the 1970s, molecular biologists and other academic scientists had assembled a group of techniques that could be applied to alter the process of drug

---

[56] On the relations between the sciences of chemistry and biology in academic and industrial contexts, see Nobel Prize-winning biochemist Arthur Kornberg's The Golden Helix: Inside Biotech Ventures, Sausalito, CA: University Science Books, 1995; esp. ch. 1. Kornberg argues that the "two cultures" are complementary, that the 'artificial' social distance between them impedes scientific and medical progress, and that future innovative successes in pharmaceutical development will be based on collaborations between chemists and biologists.

development. They had begun to learn how to engineer biological substances and processes in unprecedented ways. Some would soon learn how to engineer innovative social organizations, as well, and to create a novel entrepreneurial, scientific, and commercial culture in the spaces between universities, academic research institutes, and the pharmaceutical industry.

THE VENTURE CAPITAL INDUSTRY

The maturation of the U.S. venture capital industry is a final historical current that deserves special mention as a factor contributing to the commercial development of biotechnologies.[57] Just as pharmaceutical companies in their formative years – the latter decades of the 19th century – relied on funds made available by the contemporaneous emergence of the investment banking industry, biotech entrepreneurs and biotech start-ups in the 1970s depended, as they still do today, on financial resources made available by the evolution and growth of the venture capital business. The spectacular rise of the biotech industry in San Diego from a single tiny company in 1978 to a thriving, world class 'industry cluster' at the turn on the 21st century was made possible, in part, by economic winds that deposited concentrations of venture capital on the West Coast after World War II.[58] Venture capitalists have

---

[57] Histories of law and public policy in a range of areas (e.g., intellectual property, corporations and securities, competition and antitrust, taxes, and technology transfer) would be directly relevant, too, but won't be included. As far as the relative importance of antecedent conditions or 'causes' is concerned, the choice is arbitrary.

[58] This section is based on various scholarly and popular works examining the history of risk capital investment, the economic functions of venture capital, and the venture capital industry as a social institution, including Allan R. Ferguson, "Fueling Dreams into Reality: A Venture Capitalist's Perspective," pp. 91-103 in The Business of Biotechnology: From the Bench to the Street, ed. R. Dana Ono, Boston: Butterworth-Heinemann, 1991; Paul A. Gompers and Josh Lerner, The Money of Invention: How Venture Capital Creates New Wealth, Boston, MA: Harvard Business School Press, 2001; and The Venture Capital Cycle, Cambridge, MA: MIT Press, 1999; Christine Cope Pence, "The

played important catalytic roles in the establishment and success of commercial biotechnology wherever it has settled and prospered, and San Diego is no exception.

The presence of venture capitalists in California is certainly one of the reasons why the San Diego biotechnology industry emerged where and when it did. Strictly speaking, however, it would be a mistake to say that venture capital has driven innovation in 'technoregions' around the U.S. because it can also be said that high tech innovation has driven the formation of venture capital funds in this country. Venture investing is a high-risk proposition. Unlike debt-financing and the provision of interest bearing loans, venture capital is provided in exchange for equity and the promise of supra-normal rewards in the form of increasing valuations of ownership shares. Success in venture investing demands the consistent identification of entrepreneurial firms that will generate extraordinarily high returns. Only companies and technologies undervalued because of the high degrees of uncertainty surrounding their futures can perform in this way financially. Because rates of failure will be high among young, untested firms and technologies that fit into this category, the returns

---

Making of a Investment Decision: The Venture Capitalist's Case," Ph.D. dissertation, University of California, Irvine, 1981; Robert C. Perez, Inside Venture Capital: Past, Present, and Future, New York: Praeger, 1986; Martha Louise Reiner, "The Transformation of Venture Capital: A History of Venture Capital Organizations in the United States," Ph.D. Dissertation, University of California, Berkeley, 1989; W. Keith Schilit, Dream Makers and Deal Breakers: Inside the Venture Capital Industry, Englewood Cliffs, NJ: Prentice-Hall, 1991; and U.S. Congress, Joint Economic Committee, Climate for Entrepreneurship and Innovation in the United States, Joint Economic Committee Hearings, Ninety-Eighth Congress, 2nd Session, August 27-28. For descriptions of the roles played by venture capitalists in the formation of high-tech industries in particular, see the cases presented by Martin Kenney and Richard Florida in "Venture Capital in Silicon Valley," pp. 98-124 in Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, ed., Martin Kenney, Stanford, CA: Stanford University Press, 2000; Stephanie Jones The Biotechnologists and the Evolution of Biotech Enterprises in the USA and Europe, Houndmills, Basingstoke, Hampshire: Macmillan, 1992; Robert J. Kunze, Nothing Ventured: The Perils and Payoffs of the Great American Venture Capital Game, New York: Harper Business, 1990; and John W. Wilson, The New Venturers: Inside the High Stakes World of Venture Capital, Reading, MA: Addison-Wesley, 1985.

generated by the relatively few successes among them must be enormous in order to compensate investors for their regular losses.[59]

So, pools of venture capital usually coalesce only where sufficient streams of risky but innovative start-ups with the potential for delivering prodigous capital gains have been established or are waiting to be established. Only reasonable chances to win big jackpots can justify continued high-risk venturing. In the U.S. and in the state of California during the latter half of the 20th century, these kinds of investment opportunities were found in centers of sustained scientific and technological innovation. Venture funds skimmed from accumulations of American wealth have been drawn to centers of innovation, just as innovations made in these places have sought risk capital to feed themselves and their development. Neither innovation nor venture capital push the other in any exclusive or well-defined manner. It is impossible to portray in a cause and effect model the historical relationship between the emergence of high tech progress and the rise of the contemporary venture capital industry in the U.S. and in California. Both of these trends preceded the inception of the biotech industry in San Diego and elsewhere, but neither can be isolated as an independent causal factor of subsequent events because, from their first appearances, the two went hand-in-hand. They originated and evolved together within broader national and international economic processes.

---

[59] For a brief illustration of the mathematics of risk financing, see Dennis E. Shasha, "Venture Bets," Scientific American, 287, 3, September 2002, p. 100. The logic that Shasha describes is purely theoretical and abstract. The article's examples assign probabilities of success and failure to entrepreneurial ventures in order to highlight and clarify rationales for allocating risk capital in various ways. In the real world, of course, it is never possible to calculate these odds with precision. Far too much always remains unknown, even in (apparently) stable environments.

The U.S. venture capital industry, as it exists today as a body of established practices, organizations, and associations, is a new and unique animal. Venture investing has long history stretching back to antiquity, but its present form in the U.S. reflects a series of adaptive solutions to problems specific to the financing of high tech innovation as it developed over the course of the 20th century.[60] Martha Louise Reiner has written the richest available history of U.S. venture investing on a broad national scale.[61] She reports that the creation and institutionalization of a recognizable, professionalized venture capital industry did not begin until after World War II. Before this time, Reiner says, the character of U.S. risk venturing was very different. Through the 1920s, opportunities for purchasing equity in innovative enterprises were pursued mainly by wealthy individuals (known today in high-tech circles as 'angels'). Speculative gambling was a fashionable pastime among rich industrialists during this optimistic period, and a proliferation of high-risk investments contributed to the instability of the financial system and the great stock market crash of 1929. After the crash, funding from wealthy individuals virtually disappeared. As fortunes eroded, investors became psychologically subdued and given to extreme risk aversion. For many, the protection and preservation of capital became as important as its creation or expansion. Investment bankers, an occasional secondary source of venture funds, also became more far more timid in the post-crash environment. Growing fonder of safe

---

[60] Stories of venture investing figure centrally in the histories of all the world's 'great' empires and civilizations. Invariably, notable centers of human culture have been notable centers of human commerce built on the dedication of wealth to uncertain trading expeditions.

[61] Martha Louise Reiner, "The Transformation of Venture Capital: A History of Venture Capital Organizations in the United States," Ph.D. Dissertation, University of California, Berkeley, 1989.

bets, they lost interest in risky projects, and their involvement with entrepreneurial businesses became infrequent.

In addition, as Reiner tells, New Deal recovery policies inhibited private equity investment and encouraged conservative debt financing. The introduction of government regulation of securities trading, the enactment of heavy and progressive income and capital gains taxes, along with tax shelters and exemptions created for public bond purchases and holdings, combined to encourage capital to flow toward municipal offerings and away from innovative private enterprises. At the same time, the expansion of corporate capitalism and corporate research programs meant that a larger percentage of innovative industrial projects were sponsored internally with corporate monies and government support. Taken together, these conditions served to hamper private investments in uncertain enterprises. They generated multiple disincentives to high-risk allocations of capital. Further, as Reiner points out, industrial innovation was becoming more sophisticated. The financial hazards associated with supporting it became harder for individuals and institutions to assess without the benefit of specialized technical knowledge. The economic and political climate of the 1930s inhibited the formation of venture capital firms of the kind that would later be organized to combat this problem by providing screening and evaluation services to limited partners, for a fee and a percentage of returns.[62]

All of this changed after World War II. Among factors contributing to an environment favorable to entrepreneurship, innovation, and venture investing in the

[62] Reiner, "The Transformation of Venture Capital," ch. 2.

post-war period, Reiner cites the economic recovery and technological advances produced by the war effort, business opportunities in the reconversion of wartime production facilities and capacities, tax reforms, accumulated pools of savings, and pent-up consumer demand.[63] The first venture funds organized to take advantage of these new conditions appeared on the East Coast. Almost immediately following the conclusion of the war, in the first half of 1946, Jock Whitney, Laurance Rockefeller, Richard K. Mellon each founded entities dedicated to funding innovative enterprises with portions of their inherited fortunes. These organizations resembled contemporary venture capital firms in that they borrowed investment bankers' formal evaluation techniques and conducted independent research on investment opportunities, and, in addition, provided business assistance to entrepreneurs beyond the provision of capital. According to Reiner, the common goals of Whitney, Rockefeller, and Mellon included "achieving high returns with a high-risk investment strategy, reducing a heavy tax burden, creating a more effective way to finance innovative ventures, and benefiting society."[64] She also asserts that there was an ideological dimension to their activities. Flush with the success of the nation's recent military triumph, opposed to what they considered undue governmental control of capital during the New Deal, and annoyed by the rigidity of financial institutions beholden to the interests of large corporations, these industrials intended with their venture funds to foster and

[63] Reiner, "The Transformation of Venture Capital," pp. 125, 127.

[64] Reiner, "The Transformation of Venture Capital," p. 136.

demonstrate the economic power and the social merits of individualism, free enterprise, and private capitalism.[65]

The first venture capital organization to raise funds from investors was established in Boston, in June of 1946, by Karl Compton, president of the Massachusetts Institute of Technology, and a group of New England industrialists. The company was called the American Research and Development Corporation. Its principal goal was to fund the commercialization of technologies invented at MIT and nearby scientific institutions. Numerous technological works-in-progress at these institutions had been initiated during the war years and run on government money. Significant advances had been made, and many inventions, particularly in electronics, were approaching 'market-readiness.' After the war, government funding was reduced and projects languished. Scientists, engineers, and university administrators (at MIT, at least) with interests in commercializing new technologies to which they held rights of ownership, and business leaders recognizing that broad economic benefits could follow from regional investments in technological development, decided to establish an institution for securing support from the private sector. The company was similar to contemporary venture capital operations in that it utilized ties to local universities and relied heavily on specialized technical advisors to evaluate potential investments in 'longhair' projects. It also banked on a few successes to make up for many failures. (ARD's biggest hit was Digital Equipment Company. Eventually worth $355 million, it accounted for nearly half of the company's gains in

[65] Reiner, "The Transformation of Venture Capital," ch. 3.

its twenty-six year history). ARD's fundraising, however, had little in common with later venture capital practices. The company was structured as a closed-end mutual fund marketed mainly to individuals (institutional investors had been approached, initially, but most had declined the offer). ARD did not distribute cash or stock to investors after liquidating equity holdings, as venture capital funds do now. Instead, it issued a limited number of publicly traded shares.[66]

Through the 1960s, most venture investment organizations either followed the ARD closed-end mutual fund model or raised money as Small Business Investment Companies (SBICs), organizations that received tax breaks, loans, and matching grants from the government. The SBIC initiative was undertaken in 1957 following the launch of Sputnik. It represented a federal effort to jump-start venture investing in technology projects in order to remain competitive internationally in the space race, the arms race, and economically. SBICs sparked a great deal of interest in and experimentation with risk capital. Investments made with SBIC funds, however, remained relatively small in scale. SBICs were also hindered by complicated bureaucratic accounting requirements, and the program's success was often overshadowed by fraudulent practices that it sponsored inadvertently. At the same time, securities regulations imposed serious operational limitations on closed-end funds. Many wallowed in mediocrity, and a few suffered disastrous and well-publicized losses. Without a reliable vehicle for delivering supra-normal returns, risk capital remained a field for gamblers. The explosive growth experienced by the

---

[66] Paul A. Gompers, and Josh Lerner, The Money of Invention: How Venture Capital Creates New Wealth, Boston, MA: Harvard Business School Press, 2001; pp. 88-89.

venture capital industry in the late 1970s and 1980s followed the appearance of new investment opportunities in the formation and development of high tech industries on the West Coast, and the creation of novel investment and fund management practices by venture capitalists drawn to them. As these happenings unfolded, structural problems that had previously constrained the expansion of risk capital were dissolved. Leading venture capital firms began to establish records of spectacular, but, even more important, consistent profits. These successes changed minds about the character of risk venturing. Repeated demonstrations of twenty five percent compounded returns spurred an influx of large amounts of cash from the traditionally conservative institutional investors that manage the wealth of the nation – large banks, Fortune 500 corporations, endowments, and pension funds.

West Coast venture investing was, for all practical purposes, until at least the 1970s, synonymous with San Francisco Bay Area venture investing. The initial formation of risk capital on the West Coast was rooted in the development of the electronics industry in the Santa Clara Valley. The Santa Clara Valley is an expanse of rolling hill country situated beneath the Santa Cruz Mountains along the southernmost reaches of San Francisco Bay. Since the early 1970s, it has become better known as Silicon Valley.[67] Many of the microwave tube and solid state transistor technologies that originally gave rise to Silicon Valley were developed at nearby Stanford University. There, the promotional efforts of Frederick Terman, the legendary dean of engineering at Stanford, now often hailed as the 'father' of the

[67] As an industrial region, Silicon Valley now extends northward from San Jose in Santa Clara County through Palo Alto to San Carlos in San Mateo County.

Valley, were instrumental in the formation of the local industry in its early days.[68] Terman encouraged Stanford students and faculty, and others as well, to commercialize inventions locally. He played an influential role in the founding of such companies as Hewlett-Packard, Varian Associates, and Shockley Semiconductor, and he eventually persuaded the university to establish a high-tech industrial park on its own property, in order to facilitate academic-industry interactions.

Due largely to Terman's effective networking and his determination to build Stanford's graduate engineering programs, the federal government supplied funding that sustained electronics research at Stanford before, during, and after World War II. When research projects reached fruition, the scientists and inventors in Terman's charge typically utilized his network of contacts to transfer them to industrial settings.[69] Modest funding to commercialize technologies emerging from Stanford and the labs of private firms in the area, was available to entrepreneurs from angels and informal groups of backers in San Francisco's financial community. These local resources were sufficient to give the new industry a start. However, in order to secure funding for industrial expansion at higher orders of magnitude, entrepreneurs were

---

[68] See Robert Kargon, Stuart W. Leslie, and Erica Schoenberger, "Far Beyond Big Science: Science Regions and the Organization of Research and Development," pp. 334-354 in Big Science: The Growth of Large-Scale Research, eds. Peter Galison and Bruce Hevly, Stanford, CA: Stanford University Press, 1992; and Reiner, "The Transformation of Venture Capital," pp. 238-257.

[69] Stuart W. Leslie, "The Biggest 'Angel' of Them All: The Military and the Making of Silicon Valley," pp. 48-67 in Understanding Silicon Valley: The Making of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000; Gerald Nash, The American West Transformed: The Impact of the Second World War, Bloomington, IN: Indiana University Press, 1985.

obliged, initially, at least, to knock on doors 'back east.'[70] Organized venture investing remained largely an East Coast phenomenon for some time after the war. Eventually, though, as a critical mass of researchers, technologies, and evident successes began to coalesce in the region, and investment opportunities began to proliferate, local venturing became more cohesive, vigorous, and professionalized.

As Reiner emphasizes, West Coast venture financing was distinctive in character from its inception. Removed from the influence of conventional institutional finance in the East, it was less bound by tradition and less explicitly and self-consciously ideological. It was not concerned with stemming economic declines in decaying industrial corridors or expediting military reconversions in order to improve the general health of industrial capitalism. West Coast venture capital began with investors hunting for opportunities on the cutting edge of progress in the sciences and engineering. This activity emerged as an organic response to the technological ferment brewing around Stanford and Palo Alto. The new venturers raised funds in order to chase the success of high-profile technology firms, companies with names like Hewlett-Packard, Ampex, and Raychem. Of these companies, the reasons why they encouraged the formation of risk capital, and their peculiar characteristics as entrepreneurial projects, early Bay Area venturer William K. Bowes, Jr. says: "They were visible as companies whose investors made a lot of money and as durable companies, not just a flash in the pan...They were all in very different businesses, but

[70] Martin Kenney and Richard Florida, "Venture Capital in Silicon Valley: Fueling New Firm Formation," pp. 98-123 in Understanding Silicon Valley: The Making of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000.

they were all in technology, with engineers as founders, as opposed to businessmen."[71] A narrow focus on innovative technologies and the related necessity of working closely with entrepreneurs with backgrounds in the sciences and engineering shaped the West Coast style of venture investing and distinguished it from the more traditional approach that characterized East Coast venturing.

The West Coast approach was relatively informal. Unlike the East Coast financiers who wired funds west to the Valley, the indigenous Bay Area venture capital community sprang up and developed within the collegial networks that linked the region's scientists, engineers, entrepreneurs, industrialists, bankers, lawyers, real estate developers, universities, high-tech start-ups, and so on. Henry A. McMicking, one of the Bay Area's first venture capitalists, recalls being alerted to investment opportunities "by hearing things, by word of mouth, by reading the papers, and just by being associated with people – they mention something and you take a look."[72] On the one hand, West Coast venture capitalists were professionals who employed the research-based evaluation and screening techniques applied by investment bankers. In this way, they overcame problems that confronted part-time angels attempting to evaluate sophisticated 20th century industrial processes, or worse, technological innovations taking wing from late advances in the sciences. On the other hand, their methods were very personal in nature. West Coast venture capitalists made themselves technically astute to the extent that they could, but they also made it their business to cultivate relationships with experts that they could consult or recruit as

[71] Quoted in Reiner, "The Transformation of Venture Capital," pp. 228-229.

[72] Reiner, "The Transformation of Venture Capital," pp. 218-219.

business partners. Their principal tool was networking, and so, judging people was as important as judging technologies. Very little about the work was formulaic. Reiner asserts that West Coast venturers were consequently somewhat less preoccupied with control of the companies in which they invested than were their Eastern counterparts, and more inclined to treat relationships with entrepreneurs as egalitarian partnerships. They understood that "it is important to monitor a venture without alienating the entrepreneurs whose specialized knowledge often is its most important asset."[73] They also recognized the benefits of cooperating with other venturers. As the electronics, semiconductor, and computer industries of Silicon Valley prospered and expanded, many of the region's leading venture capital firms took up residence on Sand Hill Road in Palo Alto, in close proximity to each other. Syndication has ever since been a hallmark of technology investing in California.

Today, some old-timers grumble that number crunching MBAs have taken over the venture capital business, and that the personal and collegial aspects of the industry are disappearing. Entrepreneurs sometimes concur, and dispute venture capitalists' claims that control is not their paramount concern. They occasionally refer to venture capitalists as 'vulture capitalists' and 'company-nappers.' Still following the impressive rise of Silicon Valley, the West Coast style became broadly influential. Its success and reputation were solidifed in the mid-1970s when the leading participants in the industry adopted the limited partnership as an organizational form.[74]

---

[73] Reiner, "The Transformation of Venture Capital," p. 243.

[74] Another event that encouraged institutional investors to get mixed up in risky business occurred in 1979, after many venture capitalists had already begun to allocate significant portions of their funds to biotechnology companies. At that time, the Department of Labor reviewed the 'prudent man' rule

This innovation prompted the entry of institutional investors and their massive bankrolls into risky technology venturing. When combined with stable rates of technological innovation in places like Silicon Valley, the continuous creation of new investment opportunities, and regular success stories that whetted public appetites for profits while muting perceptions of risk, the influx of institutional funds led to a dramatic expansion of the venture capital industry in the late 1970s and early 1980s (just as new biotechnologies were appearing on the industrial scene).

In the limited partnership model, funds are raised from investors, the limited partners, then placed and managed by the general partners and associates, the venture capitalists. The venture fund remains private, no shares are traded on the open market, and the partnership is dissolved when the general partners return proceeds, in the form of cash or shares in holdings (less fund management fees and a small percentage of profits), to the limited partners. Today, all major venture capital firms are limited partnerships primarily because this structure affords two big advantages in terms of monitoring investments and disbursing capital gains to investors. First, limited partnerships that raise funds from large institutional investors (or a relatively small number of wealthy individuals) are exempt from securities regulations designed to minimize opportunistic insider trading. These regulations restrict the degrees of oversight and influence that managers of closed-end funds can exert on management.

---

attached to the Employee Retirement Income Security Act. The rule circumscribed the risks to which pension funds could be exposed. After it was decided that portfolio diversification could be considered in interpreting the rule, and that high-risk placements could be deemed prudent if they constituted only a small percentage of total investments, the volume of institutional monies flowing through venture capital firms increased substantially. As trustees of pension funds withdrew some of their monies from blue chip stocks and bonds, billions of additional dollars were made available for investments in entrepreneurial ventures. By 1983, the number of firms raising venture capital funds had multiplied

But because venture capitalists in a limited partnership are exempt, they can become directly involved in and closely monitor the management of their investments.[75] In fact, if the venture capital firm is the majority stakeholder in a private company, it may legally assume full operational control. Second, because the limited partners can elect to receive ownership shares rather than coin when the general partners liquidate a holding, they have greater control in cashing out their investments. They can time stock sales to minimize tax burdens. For these reasons, the limited partnership is a structure attractive to institutional investors and preferred by venture capitalists.[76]

When West Coast venture capitalists got involved with biotechnologies in the 1970s, they naturally followed the models provided by the semiconductor, microelectronics, and computer industries of Silicon Valley.[77] Through concrete practical experience in nurturing young high-tech companies, they had refined their methods and the ways in which they established and maintained relationships with entrepreneurs and investors. They had already established a set of practices,

---

fivefold. See Gompers and Lerner, The Money of Invention, p. 93. Biotech start-ups across the land, including the begattings of Hybritech and many others in San Diego, were among the beneficiaries.

[75] The exemption is granted because the financial stakes of limited partners in a venture fund are not vulnerable to risk and cheating in the same way as 'ordinary' individual investors may sometimes be. Unscrupulous venturers might raise funds by disguising risks that the naïve or those with modest stakes can ill-afford. The rules assume that wealthy individuals or trustees of endowments and pension funds are in positions that enable or require the diligent professional policing of investments.

[76] Gompers and Lerner, The Money of Invention, ch. 5.

[77] There are some salient differences between biotechnology and the electronics, computing, and infotech industries. Perhaps the greatest is evident in comparisons of product development timelines in the respective fields. Pharmaceutical products may take a dozen years or more to bring to market. In the other fields, obsolescence sometimes threatens technologies in a matter of months. However, rates of innovation may finally be slowing in computing – not because technical limits loom, necessarily, but rather because limits of demand may appear for numerous reasons. It is not clear that the PC market, for example, will continue indefinitely to sustain the costs of higher speeds or expanded memories. See Michel Marriot, "For PC Buying, A New Picture," New York Times, March 6, 2003. At the same time, as competition heats up in biotechnology, the turnover of advantages afforded by innovations may be

conventional means of organizing funds, structuring deals, and overseeing portfolio firms. They had already learned how to review business plans for high-tech companies, assess or establish the proprietary positions of novel technologies, project the dimensions of markets for innovative products or services, and estimate the value of ideas and unproven techniques. They had settled on standard terms of compensation for themselves and their partners. They had instituted regular patterns of syndication in order to pool financial and intellectual resources and distribute risks. They had incorporated mechanisms of control into their deals in order to protect investments, including staged disbursements of funds triggered by performance milestones and representation on company boards. They had learned how to manage inherent conflicts of interest with limited partners and entrepreneurs (conflicts having to do usually with control and compensation). They had formulated standard covenants and restrictions for themselves and their business partners, contractual checks and balances designed to discourage opportunistic behavior. They had navigated high-tech companies through the rigors of the product development process. And they had devised and honed exit strategies, conventional means of liquidating investments, terminating partnerships, and cashing out. All of these industry practices the venture capitalists adapted to the peculiar exigencies of biotech R&D. Venture capital had evolved over time as a social institution, and this historical development influenced the manner in which biotechnology companies were funded.

---

accelerating, especially in areas of research where firms and resources cluster, for instance, in the development of specific technology platforms or treatments for specific diseases.

The maturation of venture investing as a social and economic institution after World War II was crucial to the development of biotechnology in San Diego. Venture capitalists provided the funding that sustained biotechnology companies in their infancies and through their adolescent stages until they could fend for themselves (or until it became clear that they could not and needed to be sold). But the West Coast venturers were not merely passive suppliers of capital. They also attempted to 'add value,' as business folk are wont to say. They provided experience and business acumen. They mentored and dispensed advice to entrepreneurial bioscientists. They gave entrepreneurs lessons in how to run small, high-risk, but potentially high-return businesses. Although rarely involved in day-to-day management, the venture capitalists were often deeply engaged in the steering and oversight of new firms, usually from influential positions on boards of directors. Because their involvement was so often central and pivotal to successful biotech companies in San Diego, some venture capitalists deserve credit as entrepreneurs themselves. Certainly, this was the case with Hybritech and a number of its begattings.

Through these kinds of activities, venture capitalists made significant contributions to the formation of the entrepreneurial culture that characterizes the San Diego industry and accounts for much of its vitality. In the beginning, established venture capitalists were extensively 'networked' in ways that entrepreneurial bioscientists typically were not. To young biotech companies, venture capitalists often brought news of the world and access to the many forms of specialized expertise and assistance that small firms require at successive stages of development. They flipped through their rolodexes to connect executives in portfolio companies with additional

sources of funding, candidates for managerial and scientific positions, professional guidance from attorneys, accountants, architects, consultants, real estate and construction firms, trade associations, suppliers, corporate partners, executive headhunters, other venture capitalists, private investors, the media, investment bankers, stock market analysts, and so on. They acted as intermediaries, as relay stations, switches, and routers in webs of communication, and they generated important signals of their own, inputs that served to catalyze and coordinate activities. The culture of scientific entrepreneurship that has helped to make vibrant San Diego a 21st century technopolis was shaped and animated, in part, by the practices of venture capitalists when they came to town and rolled up their sleeves.

ENTREPRENEURS SHOW UP FOR WORK

Many things had to happen in San Diego, and elsewhere, in order for the biotechnology industry to emerge in the city in the way that it did. In the last two chapters, I've recounted some of them. I've presented brief histories of the city of San Diego, water and transportation in California, universities and academic research, government spending on science and technology, the medical profession and medical practice, the pharmaceutical trade, the FDA, Silicon Valley, high-tech industry, and venture capital. Had any of these histories, or any among a host of others not mentioned, followed different courses, then the emergence of the biotechnology industry in San Diego would certainly have unfolded in some other way, and it might not have happened at all. Without water piped in from the Colorado River and the Sierra Nevada, for instance, San Diego would not be a major city, let alone a center of academic scientific research and high-tech industrial development. And, of course,

without foundational work that put biochemistry, molecular biology, and immunology on definite paths of development during the 20th century, there would have been no new technologies for bioentrepreneurs to commercialize. But none of the histories presented above determined anything about the formation of the San Diego industry, and none, either singularly or in conjunction with others, ensured that it would, in fact, become established at all. It could have been otherwise.

The biotechnology industry in San Diego, just as in other locales, began when entrepreneurs moved to make it happen. Historical antecedents exert influences on real-time activities and processes, sometimes powerfully, but they don't dictate outcomes in a deterministic manner. Instead, they come together to define the contexts in which people act. They set the stage. They prepare the ground. They smooth the way or make the path rocky and steep, but they don't limit the ways in which people may adapt to the conditions they find on the road, and they don't preordain the success or failure of any expedition. In San Diego, possibilities and constraints inherited from the past became tangible and visible only after bioentrepreneurs started off on their routes and began reconfiguring their social and technical circumstances. History did not require the formation of a biotech sector in the pharmaceutical industry – a collection of small, entrepreneurial companies, founded by academic scientists, funded by venture capital, intended to make new drugs, but operated for years without products or profits. Only after entrepreneurs had begun starting companies did the idea become more than a flight of fancy. Previously, there had been no such thing in the world as a biotech sector of the pharmaceutical industry and no good reasons to anticipate the creation of one. Specialists in the

biological sciences could perhaps envision concrete applications of the new techniques they had developed, but there was little in the established institutional order of things to suggest what was coming next, and, in fact, there were no broad expectations for it. Even after it appeared, not all were clear about what the phenomenon actually was. Donald T. Valentine, a general partner in Sequoia Capital, a Bay Area venture firm that had scored many successes in Silicon Valley, and has since taken stakes in many biotech firms, concedes, in retrospect, that he and his associates didn't initially understand what they were witnessing:

> The position we took on biotechnology was as follows: There is no market; there are very few identified problems that are resolvable with this kind of technology, and the people currently managing these projects are research people. We probably looked at forty companies that had no management, no market identification, no product application, but were clearly interested in doing research. Terrific, but we're not in the research business. So we said to our clients, we're going to make zero investments in bioengineering. And we forecast this scenario: There will be fifty or sixty companies financed, none of them will have any sales or earn any money for three or four years of their lives, and at some point all these companies are going to collapse and the venture community is going to lose a lot of money. We were 90 percent right. Where we were embarrassingly wrong, it never occurred to us that the public would buy these companies and finance them, that you could raise money publicly for companies that had infinite losses and little damn prospect of sales.[78]

For almost all, the appearance of entrepreneurial biotech start-ups was unexpected, and, for many, the phenomenon was baffling. Failures to predict or understand were not due to a lack of knowledge concerning the technologies. Few, if any, familiar with the state of the life sciences at the time expressed doubts that biotechnologies would eventually transform the practice of medicine (and many other

[78] Quoted in Wilson, The New Venturers, p. 65.

fields of activity) in significant ways, or that the private sector would eventually exploit whatever practical uses could be made of them, but speculation about these future happenings was mostly idle, and it was overshadowed by more pressing concerns with possible environmental and safety hazards associated with recombinant DNA. Once the efficacy of rDNA was demonstrated, the potential risks and benefits of genetic engineering were roundly debated by scientists and policy-makers under the glare of media spotlights.[79] The business of biotechnology began quietly in the penumbra of these debates. Only occasionally in the mid-1970s did scientists or journalists make conjectures in print about specific medical and commercial possibilities,[80] and practical efforts to develop industrial applications began on such modest scales that they did not, at first, attract much attention or generate sustained controversies in ivory towers.[81] The first biotech companies on the scene were established without fanfare or publicity, and there was no broad recognition beyond the handful of persons involved in operating these enterprises that new economic opportunities had been created. There was certainly no inkling in the public consciousness that enthusiasm regarding the potential of biotechnical innovations

---

[79] Sheldon Krimsky, Genetic Alchemy: The Social History of the Recombinant DNA Controversy, Cambridge, MA: MIT Press, 1982.

[80] See Ananda M. Chakrabarty, "Which Way Genetic Engineering?" Industrial Research, 1976, 18: 45-50; and Bernard Dixon, "Genetic Engineering Goes Commercial," New Scientist, 1975, 66: 594.

[81] See Barbara J. Culliton,"Harvard and Monsanto: The $23 Million Alliance," Science, 1977, 195: 759-763. Corporate sponsorship of basic research and university alliances with big business were more salient issues. A 1974 agreement that awarded Monsanto commercial rights to research on tumor growth factors conducted at the Harvard Medical School set a precedent for this kind of relationship; many universities seeking to offset stagnant rates of federal funding for biological research followed suit. These arrangements received widely publicized criticism from faculty who feared the erosion of traditional academic values.

would soon generate a tidal wave of new entrepreneurial ventures in the pharmaceutical trade.

Genetic material was successfully 'recombined' for the first time in 1973, but Genentech, the first private venture to be founded on this capability, did not get underway until 1976. The company began when Robert Swanson, a venture capitalist with an eye on the life sciences, approached Herbert Boyer, a University of California, San Francisco biochemist, and one of the principal inventors of recombinant DNA techniques, with the idea of starting a company. Boyer had considered the possible commercial utility of his invention, but his initial attitude toward starting a new company, as legend has it, was skepticism. Apparently, he had thought about licensing his technology to established companies, but had never seriously entertained the notion of entering the pharmaceutical business himself (although the idea rapidly grew on him).[82] The impetus to establish an independent firm came from Swanson. Boyer recalls that Swanson "had this desire to start a company of his own, and he didn't want to start out in the usual fields in the Bay Area at the time, computers or running shoes or other things that were popular at that time. He wanted to do something different, and that was why he was looking. He had read a lot about the technology, and thought it might be useful."[83] When Swanson suggested a partnership, and assured Boyer that he could get some money to support it, Boyer

---

[82] See "Engineering the Therapies of Tomorrow," New Scientist, 1993, 24 April, pp. 26-27; Linda Marsa, Prescriptions for Profits: How the Pharmaceutical Industry Bankrolled the Unholy Marriage Between Science and Business, New York: Scribner, 1997, ch. 3-4.

[83] "Recombinant DNA Research at UCSF and Commercial Application at Genentech" [interview with Herbert W. Boyer, Ph.D.], UCSF Oral History Program and the Program in the History of the

figured that he might in this way be able to fund some postdocs and some experimental work in his laboratory. So he answered, "Sure, why not?"[84]

Swanson was the first bioentrepreneur. His judgments, decisions, and actions were novel and creative, and, in retrospect, they can be identified as the seeds of the biotech industry. Swanson had been working as an associate for a leading San Francisco venture capital outfit, Kleiner Perkins. He tried unsuccessfully to convince the firm's general partners that recombinant DNA represented a legitimate business opportunity and deserved a substantial commitment of funds. Kleiner Perkins tried to discourage Swanson's preoccupation with this particular technology, but he stubbornly refused to let it go. Swanson and the general partners agreed mutually that he ought to leave the venture capital business to pursue the project on his own, as an entrepreneur. Thomas Perkins, Swanson's boss, says of the decision: "In hindsight we should have said, 'OK, Bob,' and paid him $10,000 a month to come with a business plan. But we didn't realize the technology was far enough along...."[85] Except when otherwise occupied raising a new fund, venture capitalists are constantly on the lookout for new investment opportunities. They especially prize technologies that have the potential to revolutionize the production of goods or services in an industry. But, in the mid-1970s, few besides Swanson, apparently, recognized that rDNA could

---

Biological Sciences and Biotechnology, The Bancroft Library, University of California, Berkeley, 2001.

[84] "Recombinant DNA Research at UCSF and Commercial Application at Genentech" [interview with Herbert W. Boyer, Ph.D.].

[85] Quoted in Wilson, The New Venturers, p. 80. Kleiner Perkins rented Swanson some office space and later put in a $50,000 stake in Genentech. The firm then held a small piece of what would become a very valuable pie, but it had a chance, initially, to own the whole thing.

fit into that category, and Swanson was the first to make the possibility an accomplished fact. He was the first to capitalize on the technology.

In establishing the first biotech start-ups, Swanson and those who shortly followed his example created for themselves something that had been absent from the American pharmaceutical industry for the entire 20th century – opportunities for entering the field as new competitors.[86] The inherent conservatism of the industry's giant bureaucratic corporations prevented them from turning to biotechnologies as means of reversing declining rates of innovation in the field. Well acquainted with the difficulties of the drug discovery and development process, they were skeptical about the idea that molecular biology would immediately revolutionize the technical foundations of the industry (and, as it turns out, they were correct in this judgment). With accountability to shareholders and the bottom line foremost in mind, as ever, the large pharmaceutical corporations were reluctant to divert significant monies from more lucrative elements of their businesses, from research projects that promised more rapid returns, or from costly tasks judged more urgent from a strategic perspective. They decided to let others shoulder most of the financial risk associated with bringing new biotechnologies to maturity. The financing that kindled the early commercial growth of biotechnologies did not come, in the main, from established pharmaceutical houses. Neither did these corporations expel any great wealth of managerial talent to biotech start-ups as they began to devise commercial research operations (in the very

[86] See Martin Kenney, "Biotechnology and the Creation of a New Economic Space," pp. 131-143 in Private Science: Biotechnology and the Rise of the Molecular Sciences, ed. Arnold Thackray, Philadelphia, PA: University of Pennsylvania Press, 1998.

beginning, at least – an exodus of pharmaceutical executives to biotech start-ups would soon commence).[87]

"Big Pharma" is now heavily invested in biotechnologies. All of the major pharmaceutical corporations have developed their own in-house biotech R&D programs, and they support research in smaller firms through a wide variety of collaborative arrangments – contract research, licensing, joint research partnerships, equity participation, and marketing and manufacturing alliances as well.[88] But, early on, these corporations were reluctant to assume the risks of innovation in the field, and start-ups in their initial phases had to go it alone. Money and managerial advice came primarily from venture capitalists, and R&D operations were typically organized and directed by life scientists with academic backgrounds. Scientists and financial venturers were the people who first determined that something of practical value could be wrung from biotechnologies. They were the ones alert to the possible futures that advances in the life sciences had brought into view. But within the prevailing order that separated academic biology and industrial drug development, there were no instruction manuals, no formal guidelines, and no institutional memories to guide the technical integration of the two spheres. In order to make possible futures materialize, entrepreneurs had to build new kinds of organizations where none had existed before. They developed innovative means for promoting these new companies and acquiring

---

[87] Mark D. Dibner, "Commercial Biotech's Founding Fathers," Bio/Technology, 5, 1987: 571-572; Alfred Middleton, "Pharmaceutical Execs Look to Biotech Careers," Bio/Technology, 7, 1989: 883-888; Jennifer Van Brunt, "Executive Hiring Trends: Entrepreneurs and Managers," Bio/Technology, 6, 1988: 1023-1026.

the varied resources that would be needed to make them work. Only after scientific entrepreneurs had achieved a measure of success with their projects did the biotech industry became something to which others could point and name. By the 1970s, a set of conditions had been configured by chance as the background against which new biotechnologies would be developed in the life sciences. These conditions made it possible for the biotech industry to emerge where and when it did. But without entrepreneurs, entrepreneurial actions, and the formation of entrepreneurial cultures, the industry would not have happened. What follows is a story about entrepreneurs, entrepreneurial actions, the formation of an entrepreneurial culture, and how the biotech industry happened in San Diego.

---

[88] Alfonso Gambardella, Science and Innovation: The U.S. Pharmaceutical Industry in the 1980s, Cambridge: Cambridge University Press, 1995, ch. 6; Martin Kenney, Biotechnology: The University-Industrial Complex, New Haven, CT: Yale University Press, ch. 9.

VI. MEET THE ENTREPRENEURS

> Miracles are propitious accidents, the natural causes of which are too complicated to be readily understood.
>
> George Santayana

FROM DETROIT TO SAN JOSE

Howard Birndorf was stuck in traffic on the John Lodge Freeway in downtown Detroit, near the Wyoming Avenue exit. It was late December, 1974, and Birndorf, on his way to work as a lab technician at the Michigan Cancer Foundation, was looking out the windshield of his old, red Chevy Biscayne (nicknamed 'the Red Shark') into a driving snowstorm. He had just completed his master's thesis in biochemistry at Wayne State University, but was unsure of his direction in life. He had begun toying with a new research project beyond his thesis, but he hadn't convinced himself that he really wanted to pursue a Ph.D. At twenty-four years of age, he felt a bit aimless and frustrated by recent events in his life. The Michigan winter wasn't helping to raise his spirits, either. Birndorf thought to himself, 'I've got to get out of here.'[1] He decided at that moment that he would move to California as soon as he could manage it. When he extricated himself from the traffic jam and arrived at his job, he gave his boss two weeks notice of his departure: "I just went in and quit. I completed the drive, went into my adviser, and said, 'I'm not continuing anymore. That's it.'"[2] This was a pivotal episode in the formation of the San Diego biotechnology industry, although no

---

[1] Throughout the empirical chapters of this dissertation, quotes without citations are taken from interviews.

[2] Grant Fjermedal, Magic Bullets, New York: Macmillan, 1984; p. 93.

one, of course, could have guessed it at the time. The world's first biotech company wouldn't be founded for another year and a half. San Diego's first wouldn't appear until almost four more years had passed. And Howard Birndorf, just a lowly technical assistant in an undistinguished Midwestern research outpost, had no special plan or burning desire to continue working in science after leaving Detroit.[3]

Howard Birndorf grew up in Detroit, one of three sons in a Jewish family of modest means. His father was a sales representative for a shoe company. Birndorf admired his father. He says: "He traveled, he made a relatively meager income, yet he provided for our family, and put us all through college. And you know, he went without to do it. He was of that school." Birndorf was also impressed in a consequential way by his uncle, a doctor: "I saw him in his office, and with his patients, and he was, in my young eyes, godlike, in a sense. And he made a fair amount of money compared to my father. He and his family lived a lot better than my father and my family did, although we lived fine." After starting out as a political science major at Oakland University (located in Rochester, Michigan, a suburb of Detroit), Birndorf switched to a pre-med program for his junior year, and enrolled in a series of biology and chemistry courses. He thinks now that his idea of becoming a doctor was mainly a wish to emulate his uncle. He didn't really feel drawn to the curriculum, or to the required studying: "I wasn't particularly turned on by it. I mean, I wanted to be a doctor, but I don't think I really wanted to have to do all the work necessary to be a doctor." Birndorf maintained a B average in his classes, but his

[3] The Michigan Cancer Foundation is known today as the Karmanos Cancer Institute. Its principal claim to scientific and medical fame is the original synthesis of AZT in the laboratory of Dr. Jerome

MCAT scores were mediocre. He didn't make the final cut at any of medical the schools to which he applied. "I think part of me was happy that I didn't," he says, "because, really, in retrospect, I'm not sure I wanted to be a doctor. I just don't think it was what I really wanted to do."

Birndorf was twenty-one , and perhaps relieved that he wouldn't have to endure the rigors of medical training, but he still felt the weight of family expectations, and the need to achieve some kind of professional success. He never felt pushed in any particular direction, but says: "in my family, it was always 'go to college, become a doctor, become a lawyer.' You know, they said, 'you can do whatever you want as long as you're happy, but go to school and become a doctor.'" At the same time, Birndorf felt the pull of the 1960s counterculture. He had grown his hair long, gotten involved in some anti-war protests, and had gone to Woodstock. In 1969, he was a junior in college, and caught up in the times. He recalls that his parents were a bit concerned, but "actually were pretty good about it." Birndorf doesn't remember harboring any special antipathy toward mainstream societal values, but some of his interests and attitudes were evidently at odds with conventional career planning, and they apparently tempered his ambitions for status and professional advancement. Perhaps the contradictions of the time prevented him from settling on a definite path toward a definite goal. In any case, when he graduated from college, Howard Birndorf still didn't know what he really wanted to do.

Horowitz in 1964. AZT is the chemical analog of the nucleoside thymidine. It has been used widely as a treatment for AIDS because of its ability to interfere with the replication of HIV.

Having a biology degree in hand, Birndorf decided, eventually, that he would try out science as a vocation. He had not particularly enjoyed the textbook learning that dominated his pre-med education at Oakland, but during his senior year, he had been stimulated by independent lab studies under John Cowlishaw, a biology professor. Cowlishaw took an interest, acted as a mentor, and supervised experiments that Birndorf says "really turned me on." The young man found that he enjoyed working in the laboratory on his own: "Doing something original that nobody else had done, for yourself, that was very cool." The experience, he says, "really sort of changed my life." Casting about for something to do after graduation, Birndorf decided that maybe the scientific life, as he imagined it – respectable, but affording a fair degree of autonomy and opportunities to play around in laboratories – was one for him. His parents had paid for his undergraduate education, but Birndorf knew that if he wanted to go on to receive professional training, he would have to finance it himself. He decided to apply for a scholarship in the biochemistry program at Wayne State University in downtown Detroit. He won the scholarship, which covered tuition and books, and provided, in addition, a weekly stipend of $75.00.

Birndorf began at Wayne State in the fall of 1971, but he didn't get to spend much time at the bench and he didn't feel particularly thrilled to be there. "I did OK," he says. "I didn't really like it. You know it was really the elementary classes I was taking. It was a lot of memorizing and Krebs cycles and stuff." Things improved a bit in his second year. He hooked up with a new advisor, a young molecular biologist named John Bagshaw, who helped him set up a project for his master's thesis. For his thesis research, Birndorf described the properties of RNA polymerases in Artemia

salina, brine shrimp.[4] "Brine shrimp are pretty fascinating," Birndorf says. "They wash up on shore, they dry up, they dessicate, and they sit in these little balls for thousands of years. Then, when you add salt water to them, they hatch, they come back to life." Working with enzymes on his own in the laboratory suited Birndorf well at the time. He became a lab rat:

> It was interesting. I spent all kinds of hours in the lab. I liked to work at night when nobody was around, so I could use the equipment. I remember my friends were all pretty amazed that I was spending so much time down at the lab, but I enjoyed it. I just enjoyed being down there, doing my experiments. I never felt that I was a really creative scientist, but I could do the technical part really well. It's funny – somebody went back and repeated my experiments, and the results all came out perfectly, so I was good, technically.

While at Wayne State, Birndorf picked up a full-time job down the street at the Michigan Cancer Foundation. He was able then to earn more money, and he was also allowed some scheduling flexibility so he could continue to take his graduate courses. He was hired as a technical assistant in the Foundation's virology lab, and he found the work interesting and exciting: "We were doing really neat stuff. I really like viruses and molecular biology. That really turned me on. And cancer." Birndorf also got on well with the head of the lab, a Jesuit priest named Justin McCormick. "He was a really neat guy," Birndorf remembers. "I had a pony tail. I was sort of a hippie at the time, but you know, he didn't care about any of that. He was really pretty cool." For the next year and a half, Birndorf's life consisted mainly of shuttling between

---

[4] H. Birndorf, "The solubilization and characterization of DNA-dependent RNA polymerase from artemia salina," master's thesis, Wayne State University, 1974; H. Birndorf, J. D'Allesio, and J. Bagshaw, "DNA dependent RNA polymerase from Artemia embryos; characterization of polymerases I and II from nauplius larvae," Developmental Biology 45, 1, July, 1975: 34-43.

Wayne State, the Michigan Cancer Foundation, and a rented house on a lake in the suburbs, doing his scientific work and hanging out with his friends.

The following summer, this routine was disrupted by events that hastened a turning point in his life. First, Birndorf's main circle of friends left Detroit to move to California. They went to the Bay Area together to open retail outlets for a company called Roots Shoes. Someone in Birndorf's circle had a connection with the owner. The company had been started a year earlier in Toronto. Its products competed with fashionable 'negative heel' Earth shoes, and the firm was busy setting up distribution networks around the U.S. and Canada. So, his friends were off on what seemed like an exciting adventure, while Birndorf remained behind. "They all left," he says, "and I was feeling pretty alone." Then, late in the summer, as he was finishing up his master's thesis, his father suffered a massive heart attack that nearly killed him. As the year deepened, his father recuperated slowly. The son was shocked to see his father's vitality vanish so suddenly, and he grew increasingly dissatisfied with his own circumstances. Birndorf now attributes much of his general discontent to his father's condition and the feeling of helplessness that it produced: "You know, when I think back about it, it wasn't obvious at the time, but I had to get away. I couldn't stand seeing him like that." And so, one day in late December of 1974, Howard Birndorf sat in his old Chevrolet, in a traffic jam on the John Lodge Freeway, in a snowstorm, and he resolved to flee his hometown of Detroit for golden California.

In a couple of weeks, he had sold the Chevy, taken up an offer to deliver a car from Detroit to San Jose, packed a single suitcase, and, accompanied by his cousin and his dog, headed west, California-bound, down I-94. Birndorf had never really been

out of Detroit before except for a couple of extended road trips with friends. He had never lived anywhere else. He didn't have much money, just a few hundred dollars. "I had no idea where I was going," he remembers. "I had no idea what I was going to do. I just decided that I was going to leave." He was just getting away, and the San Francisco Bay Area shortly after the magical '60s perhaps seemed a promising destination – and maybe one that also happened to be about as far away from Detroit as one could get without leaving the country. Actually, once he arrived in California, Birndorf realized that he could go a little further to escape, after all. In February of 1975, he took an excursion on the cheap to Hawaii, and there celebrated his twenty-fifth birthday. When he returned to the mainland, he spent some time with his transplanted Michigan friends. They were opening and managing shoe stores, making money, driving new cars, and renting enviable pads in Berkeley. Birndorf hung around for a while and performed some odd jobs for them, but, eventually, his money ran out and he started looking for permanent work. He scoured the want ads for laboratory gigs in the area, and applied for one in the Stanford Medical School Department of Oncology. He was interviewed and hired in the latter half of 1975 as a technician in the laboratory of Dr. Frank Stockdale, where research on the molecular biology of cancer was being conducted. Birndorf found a place to live in the South Bay Area: "First, I rented a room in this really weird house, with this guy who worked at Hewlett-Packard, an engineer, and he had guns. I got out of that because he was really weird. Then I lived in a house with a bunch of law students and other students, a student house. And we shared making food, and it was cool." With his accommodations in order, Birndorf soon settled into a familiar pattern of activity. He

became a lab rat once more. He started hanging around the medical school, sometimes using the laboratory facilities at night for his own edification and entertainment.

"I USED TO GO TO THE LIBRARY AND READ MEDICAL BOOKS"

While hanging around Stanford, Birndorf eventually met up with Ivor Royston, who arrived there for a post-doctoral fellowship in 1975. The path that led Royston to Palo Alto was very different. Birndorf struggled to find his way, but Royston knew from a very early age precisely where he wanted to go and how to get there.[5] Royston was a few years older than Birndorf. He was born in England in 1945, the eldest of three sons. Both of his parents were Eastern European Jews, refugees from Nazi invasions. His father came from Poland, and fought with three different armies during the war – the Polish, the French, and the British. Royston's mother was from Czechoslovakia. She left her home to visit England in 1938. While she was gone, Chamberlain ceded the Sudetenland to Germany in the Munich agreement. She never returned home. Her future husband came to England in the evacuation of Dunkirk. They met and married during the war. Afterwards, the family remained in England, and Royston's father resumed work in his trade as a sheet metal mechanic, and as a roofer. Royston spent a summer in his early boyhood living in and gamboling about Heever Castle, a former residence of Anne Boleyn, while his father helped to repair the roof. He also watched as his father put the top on Royal Festival Hall, constructed in the early 1950s for the coronation of Queen Elizabeth. In 1954, Royston's uncle,

[5] Although Birndorf's appearance on the Stanford scene was certainly less purposeful and more haphazard than Royston's, his prior experience in cancer research earned him his spot on Frank Stockdale's payroll.

who had escaped Poland during the war to the United States, convinced his brother to relocate to America. The family moved initially to a small apartment in Plainfield, New Jersey. A year later, Royston's father secured a job in Washington, D.C., and the family moved again, this time for good.

Royston was an outstanding student – conscientious and gifted in mathematics. He once placed tenth in a Washington, D.C. city high school math contest. He excelled in science, too, and became enthralled very early on with biology and medical science: "Even before high school, I began to focus on medicine. I used to go to the library and read medical books. I got fascinated with how the body works, and it wasn't too long before I got focused on cancer. Cancer research is the area of interest to me." Royston's childhood friend, Neil Shulman, also a professor of medicine, has said "Ivor wanted to cure cancer when he was five years old."[6] During his high school years, Royston picked up a summer job in the field he had already selected as his own future profession. He applied for an internship at Walter Reed Army Hospital through a program sponsored by the National Science Foundation, and got it. "I'm sure that had something to do with propelling me to continue," he says, "because I really enjoyed it. I enjoyed doing research, interacting with the doctors and scientists." When it came time for college, the Royston family's financial circumstances limited Ivor's choices to schools that offered him scholarships, but some top schools were willing to pay his way. He could have joined the Ivy League. He was accepted at the

[6] Ann Gibbons, "The Man Who Made Millions By Marketing Monoclonal Antibodies," The Scientist, 3, 5, March 6, 1989: 1.

University of Pennsylvania with aid, but in the end, he decided to stay at home. He matriculated at George Washington University in the fall of 1963.

In the summer after his first year at George Washington, Royston continued to accumulate research experience. He got a summer job at the Beltsville Agricultural Research Center in Prince William County, Maryland, a federal institution, and there became acquainted with some plant viruses. After his second year, he decided to apply for a position in a special program at Johns Hopkins University called the 2-5 program. Students accepted to the 2-5 program finished their undergraduate degrees at Hopkins, and then, afterwards, went directly on to the medical school. The program was exclusive. Royston was one of only twenty students offered a position. "They could see from my summer job experience that I really had a commitment to research," says Royston. "I told them I wanted to do medical research, and Johns Hopkins, like Harvard and other places like that, prided themselves on turning out academic investigators, medical researchers." Royston was doing everything the right way, and he kept working hard in Baltimore in order to open up new opportunities for himself. He breezed through the medical school curriculum. During his first year, 1967-1968, a trip to Israel produced an epidemiological study and his first scientific publication.[7] He continued to work through the summers. He snared a summer research position at the National Cancer Institute in Bethesda, and garnered more research experience in virology. After completing all of his required coursework during his first three years of med school, Royston then had a final year free for

[7] I. Royston and B. Modan, "Comparative mortality of childhood leukemia and lymphoma among the immigrants and native born in Israel," Cancer, 22, 1968: 385-390.

electives. He spent it in the laboratory, in the microbiology department, working on the association between herpes simplex virus and cervical cancer. Those investigations led to several publications.[8]

Royston graduated from Johns Hopkins in the spring of 1970. Although still very young, just twenty-five, he had put himself on the fast track in medical science. He had gotten there by pursuing his interests, employing his native talents, and focusing his energies in a single-minded fashion. He had received much help, of course, from teachers, supervisors, and collaborators, and he had assembled a valuable network of professional connections, but Royston credits his parents, too, for the early success he enjoyed. His family didn't have a lot of money, but Royston never had to level his aspirations. Of the support and encouragement that he and his two brothers received from their parents, he says:

> They wanted us to succeed and to have the life they didn't have. That was a very important driving force, I imagine. My parents made it easy for us to get our work done. They didn't overload us with chores, and we didn't have to go out and earn a lot of money. As long as we were doing well in school and studying hard, they pretty much did everything they could to accommodate us. They basically put their savings into their children's education. They lived for their children, essentially. They worked hard. My mother got a job, my father worked hard, and all of the money went into our education. Education was very important. So, their expectations were that we would go to college and probably be in some profession. No one asked me to go into medicine, but they were certainly very supportive of me becoming a doctor. For them, it was going to be a real honor to have a child

---

[8] I. Royston and L. Aurelian, "Immunofluorescent detection of herpes virus antigens in exfoliated cells from Human Cervical Carcinoma," Proceedings of the National Academy of Sciences, 67, 1970: 204-212; L. Aurelian, I. Royston, and H.J. Davis, "Antibody to genital herpes simplex virus: Association with cervical atypia and carcinoma in situ," Journal of the National Cancer Institute, 45, 1970: 455-464; I. Royston and L. Aurelian, "The association of genital herpes virus with cervical atypia and carcinoma in situ," American Journal of Epidemiology, 91, 1970: 531-538; I. Royston, L. Aurelian, and H.J. Davis, "Genital herpes virus findings in relation to cervical neoplasia," Journal of Reproductive Medicine, 4, 1970: 109-113.

> become a doctor. My middle brother's a doctor, too. He's a physician in Atlanta right now, so we have two doctors in the family. We all went to college.

Having made his parents proud by becoming a doctor, Royston set his sights on further professional goals. He needed first to put in his time as an intern and a resident. He viewed these requirements as an opportunity to get to know another part of the world. He had stayed close to home to go to school; now he wanted to go exploring a bit. He had been as far east as Israel, but he had never before been further west than his home in the District of Columbia. So, when applying for internship and residency placements, he ranked the University of California, San Francisco and Stanford as his two top choices. He was assigned to Stanford, and pleased by it, because of the location, and also because the place was known for the quality of its oncological research. He went with his first wife, Anita, a woman to whom he was married for six years (they would divorce in 1973). Royston spent two years working at the Stanford University Medical Center – a complex of light sandstone buildings featuring architect Edward Durrell Stone's signature courtyards, pools, and decorative screens. Royston, who was used to the gritty, inner-city character of the Johns Hopkins' facility in Baltimore, says "it didn't really look like a hospital to me." At the end of his residency, he returned with his wife to Washington and the NIH with plans to conduct original research. As a physician/scientist, he had the option of signing up voluntarily with the Public Health Service and receiving a deferment from the military draft. There was competition for these positions, but Royston had established an impressive scientific track record for one so young, and his Johns Hopkins, Stanford, and National Cancer Institute credentials served him well. He received the posting

and a lab to direct. His project was figuring out and describing the causal processes involved in mononucleosis. He found that lymphocytes transformed by Epstein-Barr virus become targets of the immune system. Royston recalls doing the work: "Even though I had a sponsor, I had my own lab and technicians, and I started doing my own independent research. It was quite productive. We were able to elucidate what was going on in infectious mono. That led to my first major New England Journal publication."[9]

After his three-year tour of duty with the Public Health Service (and a divorce along the way), Royston targeted board certification in internal medicine with a subspecialty in oncology as the next step in his professional development. His ultimate goal was a job in a university where he could combine cancer research with the clinical practice of medicine. Above all, he desired a position from which he could start hunting a cure for cancer in earnest. He had always been fascinated by the biology of cancer. Now, as a young investigator, he was drawn to the scientific puzzles and challenges posed by the complexities of the phenomenon, and to the great personal rewards awaiting significant contributors to the field. Further, as a physician, a healer, he felt compelled to solve the daunting problems that cancerous cells present to doctors, and to counter the horrible insults that they inflict on patients and families. Learning about cancers, how to treat them, and perhaps, someday, how to cure them, was where he had been heading for years, from early in his youth. A post-doctoral fellowship in a department of oncology at a top-flight medical school seemed the

[9] I. Royston, J.L. Sullivan, P.O. Periman, and E. Perlin, "Cell-mediated immunity to Epstein-Barr virus transformed lymphoblastoid cells in acute infectious mononucleosis," New England Journal of Medicine, 293, 1975: 1159-1163.

ticket to this destination. Royston found that his NIH research stint could be counted toward the graduate training requirements of the certification process, so he was already eligible to take the exam in internal medicine. Wherever he landed, he would be able to concentrate on his oncology training. Royston applied to Stanford because of its commitment to cancer research and its reputation for excellence in the field. The medical school immediately invited him back for two more years. He returned to Palo Alto in 1975.

While at NIH, Royston's principal area of interest and inquiry had evolved from virology to immunology. His studies on infectious mononucleosis had focused on interactions between the Epstein-Barr virus and T and B cells. He says, "I became fascinated with how the body reacted against the virus, and that's immunology – how the body reacts. So, I was becoming much more interested in immunology." And since he anticipated being able to return shortly to what he considered his true calling, oncological research, he started thinking hard about the immunology of cancer. The field was just beginning to take off. Through the middle decades of the 20th century, the emergence of the molecular approach to biology had prepared scientists to begin understanding the genetic bases of cancer, and, a bit later, the emergence of the biological approach to immunology had prepared them to start learning how the body recognizes and responds to malignant cells, or fails to do so. Downstream from basic scientific inquiries in these areas, medical and pharmaceutical researchers soon began to investigate ways of applying newly developed molecular and immunological knowledge to problems of human health. They're still doing it today. Practical medical progress has been slow, but the scientific knowledge base has been rapidly

expanding. Many cancer researchers, Royston included, hope that the scientific successes will be sooner rather than later translated into medical breakthroughs. In any event, the immunology of cancer has become a thriving, booming industry.

Investigators in both academic and industrial settings are trying to find out whether it is possible to harness, alter, or stimulate the natural functioning of the immune system in order to aid the prevention, diagnosis, or treatment of cancers. They're working to develop possible cancer vaccines, and to elicit effective cellular or humoral responses to cancerous cells that have, so far, been able to elude or overwhelm the body's defenses. Some are investigating artificial means of directing immune system components like antibodies, cytokines, and interferons to stimulate attacks on tumors by soluble complement proteins; others are trying to activate immune effectors cells like killer T lymphocytes, NK cells, and macrophrages to do the job; still more are using antibodies as delivery vehicles for therapeutic agents of various sorts. Cancer immunologists want to encourage the rejection of tumors by hosts, or to tag cancerous cells as targets for therapies, without simultaneously triggering self-destructive autoimmunity. The proposed means of accomplishing these ends rely on new understandings of biological processes as they occur at the molecular level, and on detailed knowledge of the complex structures, functions, and interactions of the immune system components that comprise these processes. Understandings of the body's regulatory mechanisms and its agents were vastly expanded by the renaissance of modern immunology that began in the 1960s. By the mid-1970s, advances in the field had opened up dozens of new lines of medical research. Because of his long-standing interest in oncology and his forays into virology, Ivor Royston

was aware of and naturally attracted to new opportunities that progress in immunology had created in cancer research, and his talents, experience, and ambitions had positioned him to enter the field at an elite level. He had moved himself onto the cutting-edge of medical science. By 1975, the Stanford University School of Medicine had become a leading center for investigations into the immunology of cancer. That's why Royston applied for a post-doctoral fellowship there, and why he accepted when an invitation was extended.

MONOCLONAL ANTIBODIES

In late 1974, as Howard Birndorf and Ivor Royston were both preparing to head West to the Bay Area, momentous events in the history of the San Diego biotechnology industry were taking place far away, overseas, in and around a British Medical Research Council laboratory in Cambridge. There, Argentine biochemist César Milstein was exploring the molecular genetics of antibody diversity. He was working with murine myeloma cells, cancerous immunoglobulin-secreting lymphocytes taken from mice, because they could be grown and sustained indefinitely in tissue cultures. Normal lymphocytes usually survive for just a few generations. Fresh supplies of clones are perpetually available from myeloma cell lines, and so, working with them affords definite advantages over normal cells in terms of preserving continuity in long-term experimental projects. Myeloma clones also manufacture homogeneous immunoglobulins. This happy accident contributed to the standardization of research in the field. In addition, spontaneous mutations in myeloma cell lines had been shown to affect the structures of these antibodies. For

these reasons, myelomas had become standards tools of the trade in Milstein's area of molecular genetics.[10]

In the course of his investigations, Milstein became intrigued by the idea of studying the binding specificity of myeloma immunoglobulins (to antigens) because he recognized that tracking antibody function would be a convenient way to link protein structures with cellular processes at the molecular level (and specifically, with genetic mutations). Unfortunately, in 1974, no myeloma lines producing immunoglobulins with recognizable antibody activity had yet been established. Myelomas could be cultivated in mice easily enough by injecting the animals with mineral oil, and researchers had learned how to maintain the cells in vitro, but there were still no procedures for selecting myeloma cells that secreted immunoglobulins specific to a definite antigen. Attempts to induce myelomas to generate antibodies of known specificity in response to immunizations had failed.

A related line of inquiry being pursued in Milstein's lab at the time presented a solution to the problem. In order to elucidate the pathways of antibody gene synthesis, Milstein and some of his colleagues had been fusing immunoglobulin-producing myeloma cells, and then analyzing and comparing the antibodies created by the hybrids.[11] In this way, cell hybridization permitted the researchers to identify the origins and physical locations of particular genes that govern the synthesis of proteins

---

[10] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995; ch. 1. For sociological discussions of the centrality of such tools in scientific work, and the ways in which they influence the directions in which scientific inquiries proceed, see Adele E. Clarke and Joan H. Fujimura, eds., The Right Tools for the Job: At Work in the Twentieth-Century Life Sciences. Princeton, NJ: Princeton University Press, 1992.

making up different parts of antibody molecules. Observing similarities and differences among the gene products of fused cells and their 'parent' cells was a method of making connections between the structural designs of antibody proteins and genetic processes taking place in cell nuclei. Biochemists and immunologists had long possessed tools that enabled them to study antibody configurations, but they were just beginning to understand the ways in which cells manufacture immunoglobulins. Milstein and other biochemists and immunologists in the field naturally began to apply techniques developed by cell biologists, like hybridization, when they decided to work backwards to identify the genetic sources of antibody diversity and specificity.[12]

The molecular structures of antibodies (of the IgG class) resemble the letter Y.[13] The Y-structures are composed of four molecular chains – two 'heavy' chains and two 'light' chains – linked together chemically by disulfide bonds. The longer heavy chains extend the full length of the Y, each stretching from the bottom of the 'upright' base to the end of one of the arms. The shorter light chains are attached to

---

[11] R.G.H. Cotton and César Milstein, "Fusion of Two Immunoglobulin-Producing Myeloma Cells," Nature, 244, 1973: 42-43.

[12] C. Milstein, K. Adetugbo, N.J. Cowan, G. Köhler, D.S. Secher, and C.D. Wilde, "Somatic cell genetics of antibody-secreting cells: Studies of clonal diversification and analysis by cell fusion," Cold Spring Harbor Symposia on Quantitative Biology, 41, 1977: 793-803; C. Milstein, "From antibody structure to immunological diversification of immune response," Science, 231, 1986: 1261-1268.

[13] There are five different classes of antibody with different sizes, shapes, and functions in the immune response. IgG is the most common (Ig stands for immunoglobulin). The others are called IgM, IgA, IgD, and IgE. IgM molecules circulate in bodily fluids and act as the body's first line of defense following exposure to an antigen. They are large (comprised of five Y-shaped monomers) and carry numerous binding sites. They are thus well-equipped for their early detection task. IgA antibodies are plentiful in mucous membranes. They serve to prevent the attachment of viruses and bacteria on the surfaces of epithelial tissues. IgD antibodies are found mainly on the surfaces of B cells where they function as antigen receptors. IgE molecules interact with mast cells and basophils, playing roles in the triggering of allergic reactions. IgG is the most plentiful antibody type. IgG molecules circulate in the blood and other fluids. They identify and adhere to bacteria, viruses, and toxins that they encounter, neutralizing the invaders or marking them for destruction by phagocytes and complement proteins.

the arm portions of the heavy chains. The lengths of the heavy and light chains are also divided into two regions defined, not by molecular shape alone, but also by biological function and by the genealogies of the peptide groupings that constitute them. The 'constant' region is so-called because it is identical in every antibody of a given immunoglobulin class. In the IgG class, the constant regions of the heavy chains include the upright base of the Y and the lower halves of the two arms. The constant region of light chains are situated on the lower halves of the arms, as well. The upper ends of the arms comprise the 'variable regions' of both heavy and light chains.

The variable regions of the heavy and light chains contain the antigen binding sites of the antibody, the molecular keys that fit precisely into the molecular locks (called 'epitopes' or 'determinants') displayed on the surfaces of antigens. They account for the enormous diversity and 'exquisite' specificity of the humoral immune response. Each immunoglobulin-secreting B-lymphocyte and its clones produce one and only one kind of antibody, one with a distinctive and highly specific variable region. The variable regions of antibodies manufactured by a particular line of clones feature definite peptide combinations that are unique. When triggered by appearances of antigenic substances in the body, the immune response stimulates the proliferation of clones from a vast number of B-cells. This results in the production of an equally vast number of different antibodies that can identify and tag, precipitate and agglutinate, and sometimes neutralize an even greater number of different antigens.

Milstein had begun fusing myelomas in order to explore the genetic bases of the structural uniformity and variability found within immunologlobulin 'populations.'

His investigations showed that, without exception, the genes controlling the 'constant' and 'variable' regions of chains manufactured by a hybrid myeloma were contributed by just one of the 'parent' cells. The hybrid cells did not produce hybrid chains. They produced some hybrid antibodies, immunoglobulins in which heavy or light chains derived from one parent were bound to heavy or light chains derived from the other, but the variable and constant regions of any given chain were always coded by the genes of a single lymphocyte precursor.[14] For instance, when Milstein and R.G.H. Cotton created rat-mouse myeloma hybrids, the cells manufactured antibody chains derived exclusively from one species or the other.[15] None of the rat-mouse cells produced 'scrambled' immunoglobulin chains, chains that combined a rat constant or variable region with a mouse constant or variable region. It was later determined that the genes coding for the proteins that make up the constant and variable regions of antibodies are located on the same chromosome in close proximity to each other. The sequences are spliced together and then transcribed by a single piece of messenger RNA. The genetic machineries of plasma cells do not normally operate in ways that allow hybrids to 'mix and match' gene sequences coding for heavy and light antibody chains.

To Georges Köhler, a German cell biologist visiting the MRC lab to study antibody diversity on a post-doctoral fellowship, Milstein's cell fusion experiments suggested a means of getting past the obstacle that was holding up the lab's parallel

---

[14] See César Milstein, "Monoclonal Antibodies," Scientific American 243, 1980: 66-74.

[15] R.G.H. Cotton and C. Milstein, "Fusion of two immunoglobulin-producing myeloma cells," Nature, 244, 1973: 42-43.

efforts to assay the antigen-binding properties of antibodies secreted by mutant lymphocytes. He had the idea of fusing a murine myeloma and a normal murine lymphocyte that manufactured antibodies targeted against a known antigenic substance. It had not previously occurred to Milstein to incorporate normal lymphocytes into his work because they could not be maintained in culture.[16] A report on a fusion of normal human lymphocytes and murine lymphoma cells had been published by Jerrold Schwaber and E.P. Cohen in the high-profile journal Nature the year before,[17] but it was not until after Milstein's research on myelomas had stalled that the accomplishment became directly relevant to work conducted in the Cambridge lab. Even when the limitations of existing myeloma cell lines had become apparent, and Milstein concluded that antibodies of predefined specificity could perhaps solve some of his problems, it was still not obvious to him that normal lymphocytes had a role to play in the next step forward. In fact, before Köhler proposed the fusion experiment, Milstein had encouraged him to conduct a laborious test of clones from one of the lab's myeloma cell lines in order to discover the antigen against which the line's antibodies were directed. Köhler later recalled that "César wanted me to make a screen to find what the P3 [the name of the cell line] antibody would bind to."[18]

Köhler's idea of employing normal lymphocytes as fusion partners with myelomas was unorthodox because cell biologists had rarely experienced success in

---

[16] N. Wade, "Hybridomas: The making of a revolution," Science, 215, 1982: 1073-1075.

[17] J. Schwaber and E.P. Cohen, "Human x mouse somatic cell hybrid clones secreting immunoglobulin of both parental types," Nature, 244, 1973: 444-447. In this experiment, the specificities of the lymphocyte parents' antibodies were unknown, and so, then, were those of the hybrid's immunoglobulins.

previous attempts to fuse normal plasma cells, and only Milstein and a very few others had managed to create myeloma hybrids.[19] Prior attempts to perform Köhler's fusion elsewhere had failed.[20] It would have been easy for Milstein to dismiss the idea as a probable waste of scarce time and valuable resources. The plan did make some theoretical sense, though, and the Cambridge lab's experience in working with myelomas, along Schwaber and Cohen's reported success in fusing a normal lymphocyte with a cancer cell, perhaps encouraged Milstein to consider it seriously. When Köhler expressed his strong preference for the strategy, Milstein agreed to let him try it. "It occurred to us," Milstein later wrote, "that it might be possible to fuse a normal lymphocyte or plasma cell with a myeloma cell and thus to immortalize the expression of the plasma cell's specific-antibody secretion."[21] This was precisely what Milstein was after as a means of moving forward the work of the laboratory.

---

[18] N. Wade, "Hybridomas: The making of a revolution," pp. 1073-1074.

[19] Influential figures in immunology and cell biology had announced that myelomas could not be fused by conventional methods. The common hybridization technique of the day employed the Sendai virus as a fusogen. In this method, an inactivated version of the virus is added to a culture medium with the cells to be fused. When a virus particle happens to infect two cells at once, it acts as a bridge across the outer membranes of the fusion partners and facilitates hybridization. The Sendai virus technique would not work with myelomas, according to Harris and Cohn, and Horibata and Harris, because myelomas "are not agglutinable by that virus." In other words, myelomas were believed to be immune from Sendai infection by virtue of the peculiar molecular characteristics of their cell surfaces. See A.W. Harris and M. Cohn, "Physiology and genetics of some lymphoid cell functions," pp.275-279 in Developmental Aspects of Antibody Formation and Structure, Vol. 1, eds. J. Sterzl and I Riha, Pragua: Academia, 1970; K. Horibata and A.W. Harris, "Mouse myelomas and lymphomas in culture," Experimental Cell Research, 60, 1970: 61-70. Melvin Cohn, the scientist who originally supplied Milstein with myelomas suspects that the treatment or care of the cells in the Cambridge lab somehow transformed them, making them agglutinable by the virus, and that this accounts for the Cambridge lab's good fortune in the myeloma fusion business.

[20] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995; pp. 24-25; E.M. Tansey and P.P. Catterall, "Monoclonal Antibodies: A Witness Seminar in Contemporary Medical History," Medical History 38, 1994: 322-327.

[21] Milstein, "Monoclonal Antibodies," p. 66.

Possessing myelomas that manufactured immunoglobulins of known specificity would enable researchers to clone out mutants and assay the binding properties of their antibodies. Milstein anticipated that the capacity to correlate gene expression with the biological functions of immunoglobulin proteins would serve as a powerful tool in the study of antibody diversity. It would make for more efficient structural and chemical analyses of proteins, while simultaneously augmenting these inquires and creating new avenues for the exploration of somatic mutations.[22]

Köhler set out in the fall of 1974 to create the lymphocyte/myeloma hybrids. He first immunized pink-eyed, white-coated, albino BALB/c mice, a standard inbred laboratory strain, against sheep red blood cells. The sheep cells were selected because they were known as good immunogens in the BALB/c 'experimental model' and antibodies against them could be easily detected in culture supernatant using a routine

---

[22] Monoclonal antibodies have proven useful in many additional areas of scientific and industrial research, and in medical practice, but Köhler and Milstein did not immediately perceive the full significance of their invention. They were initially concerned with developing tools to employ in genetics research. Only on writing up the first report of the fusion experiments some months afterwards did Milstein consider the wide applicability and potential economic value of monoclonal antibodies. He then suspended his studies of antibody genes in order to demonstrate and promote the broad utility of hybridoma technology: "it dawned on me that it was up to us to demonstrate that the exploitation of our newly acquired ability to produce monoclonal antibodies à la carte was of more importance than our original purpose...For several years I shelved the antibody diversity problem to demonstrate the practical importance of monoclonal antibodies in other areas of basic research and clinical diagnosis." Quoted in Cambrosio and Keating, Exquisite Specificity, p. 35. One of the areas in immunology to which Milstein first applied monoclonal antibodies with notable success was the characterization of T cells and their surface receptors. Hybridoma technology enabled rapid advances in this field. See C. Milstein, "The impact of monoclonal antibodies on studies of the differentiation of lymphocytes," pp. 3-8 in Leucocyte Typing: Human Leucocyte Differentiation Antigens Deteced by Monoclonal Antibodies, eds. Alain Bernard, Laurence Boumsell, Jean Dausset, César Milstein, and Staurt Schlossman, Berlin: Springer Verlag, 1984. The notoriety that Köhler acquired because of his association with hybridoma technology did not deter him from his program in genetics research. When he returned to his regular post at the Basel Institute of Immunology, he employed hybridoma technology in his studies on lymphocyte mutations, but did not explore other applications. He says, "I successfully refused...to become a monoclonal antibody maker." N. Wade, "Hybridomas: The making of a revolution," p. 1075.

immunological assay.[23] Köhler then harvested lymphocytes from the spleens of the mice and followed the lab's cell hybridization procedures. As fusion partners for the B-lymphocytes, he chose murine myelomas from Milstein's P3-X63Ag8 line. The P3 in the cell line nomenclature signified that the myelomas were the third in a series of lines furnished to the Cambridge lab by Melvin Cohn of the Salk Institute of Biological Studies in San Diego, on Milstein's request, and that the line was originally established by Dr. Michael Potter, at the National Institutes of Health in Bethesda, Maryland, in the early 1960s. X63 indicates that this particular batch of cells was the sixty-third cloned out of the P3 line, and Ag8 refers to a genetic marker that Milstein had added to it. The marker is important because it permits the sorting of fused and unfused cells following hybridization.

After selecting and preparing his cells, Köhler combined them in a selective HAT (hypoxanthine/aminopterin/thymidine) culture medium, along with inactivated Sendai virus to act as a fusogen. He knew that the growing cells he subsequently observed were hybrids because of the genetic marker that Milstein had added to the P3 line. The marker was induced by exposing the cells to a chemical called 8-azaguanine. Cells that survive exposure to 8-azaguanine are deficient in HGPRT (hypoxanthine guanine phosphoribosyl transferase), an enzyme required in order to metabolize nutrients in the HAT medium. This preparation is done in order to facilitate the kind of cell selection that Köhler needed to perform. Köhler knew that normal lymphocytes would not survive for long in the HAT medium because they

---

[23] Jerne, N.K., and A.A. Nordin, "Plaque formation in agar by single antibody-producing cells," Science 1963, 140: 405.

were generally unsuited for the environment. Neither would myelomas lacking HGPRT last very long. They would soon starve. Only successfully fused lymphocyte/myeloma hybrids having borrowed the HGPRT gene from the normal lymphocytes could be maintained in the HAT medium.

Around Christmas of 1974, after the cells had been incubating for seven weeks, Köhler conducted a test to find among the hybrids those producing antibodies against sheep red blood cell antigens. Many were discovered. Few generated true monoclonals, but, in prior work with myeloma/myeloma hybrids, Milstein had developed assays for identifying and selecting cells that secreted proteins coded exclusively by genes borrowed from just one of the parents. He and Köhler were able to isolate and establish in culture the desired monoclonal-making cells. Milstein expected, too, on the basis of his prior experience, that they would likely be able to streamline the process by performing fusions with myelomas that didn't secrete antibody or manufactured only antibody fragments.[24] It appeared to Köhler and Milstein, then, that they would be able to conduct their somatic mutation experiments with stable supplies of monoclonal antibodies specific to at least one predetermined antigen, sheep red blood cells. And they anticipated that they would be able, for the first time, to use standard immunoassays to associate the binding properties of these

---

[24] Hybrids commonly lost chromosomes and antibody chains in early stages of clonal expansion. In some cells, myeloma chains disappeared and only monoclonals were synthesized. See Milstein, "Monoclonal Antibodies," p. 69. Köhler and Milstein soon substantiated Milstein's guesses empirically, and made reports, including: G. Köhler, S.C. Howe, and C. Milstein, "Fusion Between immunoglonbulin-secreting and non-secreting myeloma cell lines," European Journal of Immunology 6, 1976: 292-295; and G. Köhler, H. Hentgartner, and C. Milstein, "The sequence of immunoglobulin chain losses in mouse (myeloma x B-cell) hybrids," pp. 545-549 in Protides of the Biological Fluids. Proceedings of the Twenty-Fifth Colloquium. Brugge, 1977, ed. H. Peters, Oxford: Pergamon Press, 1978.

antibodies with genetic mutations in the plasma cells that gave rise to them.[25] The work leading to these conclusions is described in Köhler and Milstein's famous paper published in Nature in late 1975. The paper announced the invention of hybridoma technology.[26] Many thousands of scientific papers detailing practical applications of this new technology would be published in subsequent years.

THE DIFFUSION OF HYBRIDOMA TECHNOLOGY

As sociologists Alberto Cambrosio and Peter Keating have pointed out, Köhler and Milstein made their invention by combining several techniques practiced commonly in cell biology and immunology at the time.[27] Immunocompetent cells had previously been 'immortalized.' Several different myeloma lines were available to researchers, and most of them produced some kind of functional antibody or antibody fragment. Myeloma clones were maintained in many laboratories as immunoglobulin assembly plants (although no one happened to know the particular antigens against which the antibody proteins were designed to react). Neither was there anything new about cell hybridization in the mid-1970s. Cell biologists had been fusing mammalian

---

[25] The method needed a few further refinements before it was ready for prime time. After their initial success, Köhler and Milstein experienced months of trouble during which they couldn't reliably reproduce the result. The B-lymphocyte and myeloma cells wouldn't fuse and the scientists couldn't manufacture monoclonal antibodies. The source of the problem remains unclear – contaminated reagents or an unrecorded transformation in the cell line are possible causes – but, in any event, the difficulties evaporated and hybridoma techniques were improved and routinized when Italian Giovanni Galfré arrived in Cambridge and substituted polyethylene glycol (PEG) for Sendai virus as the fusing agent. The use of PEG thereafter became standard practice among monoclonal antibody makers. See Milstein, "Monoclonal Antibodies," p. 68.

[26] G. Köhler and C. Milstein, "Continuous cultures of fused cells secreting antibody of predefined specificity," Nature 256, 1975: 495-497.

[27] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995; ch. 1.

cells since the early 1960s.[28] Hybridization techniques had been standardized and applied for many different purposes, with many different kinds of cells. A fusion of normal lymphocytes and cancerous myelomas had not been previously achieved (Melvin Cohn had attempted it at the Salk Institute),[29] but antibody-generating lymphocyte hybrids had been created, and, as indicated above, cell biologists and immunologists had been working with both murine lymphocytes and myeloma cells for some time. They knew a lot about their dispositions and characteristics, and both had been previously employed in successful cell hybridization experiments. Finally, only the steps of immunization (or otherwise stimulating antibody secretion in immunocompetent cells) and assaying for the presence of monoclonal antibodies in culture separated the 1973 human lymphocyte/murine lymphoma fusion performed by Schwaber and Cohen from an effective application of hybridoma technology.[30]

The production of monoclonal antibodies specific to predetermined antigens had already been accomplished, too. Immunologists had been conducting research with them for several years when Köhler and Milstein unveiled the hybridoma approach in 1975. Prior to the introduction of hybridomas, researchers had been applying the 'splenic fragment culture' technique developed by Norman Klinman at

---

[28] See John W. Littlefield, "The Early History of Mammalian Somatic Cell Fusion," pp. 421-426 in Cell Fusion, ed. Arthur E. Sowers, New York: Plenum, 1987.

[29] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, pp. 24-30.

[30] J. Schwaber and E.P. Cohen, "Human x mouse somatic cell hybrid clones secreting immunoglobulin of both parental types," Nature, 244, 1973: 444-447.

the University of Pennsylvania.[31] In Klinman's method, mice were immunized and sacrificed. B-cells were transferred by injection, along with antigenic cells or substances, into the spleens of live, syngeneic (genetically similar and immunologically compatible) mice that had been irradiated in order to destroy their native polyclonal immunocompetence. There, the B-cells were allowed to proliferate in vivo before being removed for processing.[32] When the irradiated mice were sacrificed, a tissue chopper was used to dice their spleens into very tiny cubes. The fragments were placed into the wells of tissue culture plates, again with antigens to stimulate antibody secretion. In some wells, colonies of active clones would expand from a single B-lymphocyte and begin secreting monoclonal antibodies into the medium. These antibodies were harvested and used for research.

Before hybridomas were invented, Klinman's splenic fragment culture technique was the only method available for isolating monoclonal antibodies. Researchers continued to employ it for a time after the Köhler and Milstein announcement for certain purposes (or if they lacked the cells or know-how required to cultivate hybridomas). In comparison to the hybridoma approach, however, the splenic fragment system had one serious limitation – the lymphocyte clones could not be kept alive in culture for extended periods. In the mid-1970s, at the Wistar Institute in Philadelphia, Walter Gerhard, one of Klinman's former students, was investigating

---

[31] N.R. Klinman, "Antibody with homogeneous antigen binding produced by splenic foci in organ culture," Immunochemistry 6, 1969: 757-759; Norman R. Klinman, Gary P. Segal, Walter Gerhard, Thomas Braciale, and Ronald Levy, "Obtaining Homogeneous Antibody of Desired Specificity from Fragment Cultures," pp. 225-236 in Antibodies in Human Diagnosis and Therapy, eds. Edgar Haber and Richard M. Krause, New York: Raven Press, 1978.

the antigenic character of various strains of the influenza virus. He employed the splenic fragment technique to produce monoclonals that recognized viral antigens, and he had managed to keep lymphocyte clones alive in vitro for about ninety days. That appeared to be the limit. Gerhard's lymphocytes were fortunate to have enjoyed such longevity, and to have had such a skillful caretaker. But when they stopped secreting their unique immunoglobulins and died, that was the end of the supply of those particular antibodies.

It was always possible to develop other antibodies to the antigen of interest through further rounds of immunization, tissue harvesting, and fragment culturing, but the genetic information that gave rise to the specific antibody that reacted with a specific epitope of the antigen in a precise way was gone with the specific clones that produced it, never to be recovered again – unless by some freak chance an identical B-cell were to be found. The odds against such an accident are astronomical, and even if it occurred, as long as researchers were working within a system characterized by short-lived antibody supplies, it probably would not have been worth the effort to establish the identity of the cell or its immunoglobulin in any thoroughgoing manner. Exercises of this kind became sensible only after the introduction of Köhler and Milstein's invention. Hybridoma technology made available continuous supplies of homogeneous immunoglobulins, but it also created novel uses for antibodies, and, simultaneously, for many researchers employing them as tools rather than subjects of inquiry, deeper interests in their molecular identities. If antibodies are needed simply

---

[32] This procedure encouraged more B-cell activity and yielded more monoclonals than either culturing tissues taken directly from immunized animals or in vitro stimulation of immunocompetent cells.

to identify antigens, hybridoma technology affords no special advantages in many instances. However, if change or variability in molecular structures over time is of interest, as in studies of cellular genetics, for example, or if repeatedly targeting the same antigenic determinant in different samples is an instrumental goal, then homogeneous immunoglobulins have value as standardized reagents. In these contexts, Köhler and Milstein's method constituted a genuine technical breakthrough. It permitted researchers to make progress where the splenic fragment culture technique did not. Its diffusion among academic and industrial scientists eventually spread to every corner of the globe, from Cambridge to Fairbanks, Osaka, Perth, Nairobi, and Punta Arenas.

Alberto Cambrosio and Peter Keating have written the definitive history of the diffusion of hybridoma technology.[33] They note that it took some time following the late 1975 publication of the Köhler and Milstein paper for the technique to become widely adopted. A lot of practical work had to be done before it could become a 'standard' protocol – one applied broadly and in more or less the same manner with comparable results. Materials and skills figure centrally in the story that Cambrosio and Keating tell about the standardization of hybridoma technology. They emphasize the artisanal character of the practice. Technical work, they argue, requires embodied tacit skills derived from practical 'hands on' experience. In order to produce monoclonal antibodies, it is not enough simply to follow a recipe, an abstract description of the kind provided in the materials and methods sections of scientific

[33] Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995.

papers. It entails learning by doing and acquiring the practical sense needed to interpret instructions and follow procedures in the proper way, a sense that inheres in familiarity with the material elements of the practice.[34]

Following the invention of hybridoma technology, many researchers and laboratories reported trouble replicating Köhler and Milstein's accomplishment, even when they had in their possession the Nature paper describing the technique and all of the necessary materials. According to Cambrosio and Keating, this was because making monoclonal antibodies is an 'art' as much as it is a 'science.' To make monoclonals successfully, technicians had to acquire special kinds of know how. They had to develop 'golden hands' – a 'touch' or a 'feel' for handling mice and cells and reagents. They had to create particular sets of material conditions, usually by trial and error tinkering, that would make each step of the process workable. They had to provide suitable environments for cell fusion, clonal expansion, and the secretion of monoclonals by the hybrids. This wasn't simple or easy when it hadn't been done before. In the beginning, before many of the bugs were worked out, and before people engaged in and teaching the practice could be found in most centers of biological science, making monoclonals was tricky. Köhler and Milstein themselves experienced difficulties making the process work consistently after their initial breakthrough. They spent many months trying to establish reliable practices. Every laboratory attempting to make monoclonal antibodies had to wrestle with the same kinds of problems and develop its own solutions and protocols in order to achieve success. Cambrosio and Keating insist that the 'universality' of hybridoma technology was created by many

---

[34] Cambrosio and Keating, Exquisite Specificity, ch. 2.

local adaptations of the general method to the particularities and peculiarities of specific people, places, physical conditions, and established social and technical habits. The eventual standardization of materials and practices that came to constitute hybridoma technology depended on communication and the coordination of actions between groups of researchers and technicians situated in many distant locales.

In addition to the transmission of knowledge and skills, the diffusion of hybridoma technology depended also on the distribution of materials. Many supplies required for the application of hybridoma technology were basic and regular components of a well-equipped biological laboratory at the time, but others, like specific antigens, breeds of mice, or varieties of culture supernatant, for instance, perhaps were not. In any case, the technology was not applied anywhere until labs were properly outfitted. In their discussion of the material diffusion of the technology, Cambrosio and Keating focus on one element in particular – myeloma cells. Any laboratory or group that heard of Köhler and Milstein's invention and wanted to start manufacturing monoclonals needed first to acquire suitable myelomas (after deciding to disrupt internal routines, pay the inevitable social and economic costs of conversion, and, perhaps, abandon old research projects for new ones).

The myelomas were indispensable, but scarce. Initially, one had to go through Cambridge in order to acquire them. As the only supplier, Milstein did his part. He made the cells freely available to credible researchers who said please and thank you, as was the custom. He began by distributing myelomas to scientists and laboratories conducting research in his own branch of immunogenetics. Reputable participants in the field could request cells and expect to receive them as a scientific courtesy. So,

acquisitions were relatively easy for those with direct connections to the source. Others lacking social and professional capital of the right kind had to wait. The Cambridge lab honored many requests for bits of its valuable property, but Milstein was not formally obliged to surrender cells. The sharing was discretionary. The diffusion of hybridoma technology required the prior diffusion of myelomas, and this was governed by social constraints. Supply determined demand, for the most part. Few lacking connections could have been planning to use hybridomas. In any event, Milstein gradually withdrew from the myeloma exporting business and left it up to others possessed of the cells to set up supply networks. A few became important 'cell brokers.' Eventually, over a period of several years, the P3-X63Ag8 line that Milstein had prepared became very widely distributed. Most of the myeloma clones employed in applications of hybridoma technology and monoclonal antibody production around the world can trace their origins back to this original source.[35]

Köhler and Milstein's invention provided the technical foundation for Hybritech, San Diego's first biotech company. In order for hybridoma technology to take root in San Diego, it was necessary first for myeloma cells and embodied personal skills in the art and science of monoclonal-making to travel there. Cambrosio and Keating tell the story of an individual who played an important part in creating the circumstances in which this became possible and did, in fact, happen. In 1976, after Köhler (back in Basel) and Milstein had ironed out the kinks in hybridoma

---

[35] Cambrosio and Keating's history charts the early diffusion of P3 cells and other mouse and rat myeloma lines from Milstein's MRC laboratory in Cambridge, Melvin Cohn's collection of cells at the Salk Institute, and several additional hybridoma cell banks that appeared between 1977 and 1981. See Exquisite Specificity, ch.3.

technology, and Milstein had begun exploring new applications for it beyond the study of lymphocyte genetics, a researcher in immunology named Leonard Herzenberg arrived at the MRC Laboratory in Cambridge as a visitor. Herzenberg was on a sabbatical leave from the Stanford University Medical School. He was in Cambridge because he knew Milstein and wanted to sharpen his skills in molecular biology.

Herzenberg was also interested in promoting the use of a device he had helped to develop in collaboration with Los Alamos engineers in the late 1960s, the fluorescence-activated cell sorter (FACS).[36] The FACS is a kind of flow cytometer. It works by injecting cells of various kinds through a narrow chamber, where they are scanned by a laser. The cells have fluorescent dyes attached. Each type of cell is matched with a dye that will give off light at a particular frequency when scanned. As cells pass in single file through the chamber, the laser beam excites the fluorochromatic dyes. The characteristic emissions are measured by a light detector. In this way, quantitative data on every cell, each category of cell, and the composition of entire samples can be recorded and analyzed. (Many doctors became familiar with the FACS in the 1980s after they began to understand the mechanisms of HIV infection and accepted T cell counts in blood samples as markers for the progression of AIDS. The device was employed to sort out $CD4^+$ T cells from other kinds of cells and to record their numbers). Just prior to his arrival in Cambridge, Herzenberg and Stanford University struck a deal with medical device and supply company Becton-Dickinson to manufacture and market the FACS.

---

[36] Cambrosio and Keating, Exquisite Specificity, pp. 91-95.

As Cambrosio and Keating tell it, Milstein was not particularly enthused about the FACS. He saw no special call for it in his genetics lab. Herzenberg, however, was quite taken by hybridoma technology, for two reasons. First, he recognized that monoclonal antibodies could be employed to make the operation of the FACS more efficient, precise, and reliable.[37] The use of antibodies with a high degree of specificity for a type of cell and/or a type of fluorochrome improved cell-tagging procedures, made it easier to prepare numerous cell types for analysis, and reduced sorting and counting errors. Second, Herzenberg recognized that hybridoma technology promised something that, in his opinion, immunology then needed sorely – standardized reagents. Having witnessed countless disputes among colleagues regarding the equivalence of materials and the comparability of experimental findings, he saw the diffusion of homogenous monoclonals as a means of coordinating investigations and speeding cumulative advances of knowledge in immunology, cell biology, and related fields. In the case of fluorescence-activated cell sorting, Herzenberg saw that the use of monoclonals would permit the establishment of universal testing benchmarks.

In the years following his sabbatical in Cambridge, Herzenberg became very active in promoting, not only the FACS, but also applications of monoclonal antibodies for various purposes in many different areas of research. He wrote papers and organized conferences to spread the word about the general utility of hybridoma technology and value of monoclonals as serological reagents. And in the earliest days

---

[37] L.A. Herzenberg and J.A. Ledbetter, "Monoclonal antibodies and the fluorescence-activated cell Sorter: complementary tools in lymphoid cell biology," pp. 315-330 in The Molecular Basis of Immune Cell Function, ed. J. Gordin Kaplan, Amsterdam: Elsevier/North Holland Biomedical Press, 1979.

of hybridoma technology, he was also involved in distributing Milstein's myeloma cell line. It was Herzenberg's objective to make monoclonal antibodies generally available.[38] Supplied with myelomas and knowledge of the fusion procedures, researchers would be able to make and share with colleagues antibodies specially designed for the objects and problems that defined their respective fields. When Herzenberg returned to Stanford at the end of his sabbatical year, he carried Milstein's myelomas with him. He soon started passing them out to interested medical school faculty. In the summer of 1977, the Stanford University Medical Center became one of the few places in the world that hybridomas and monoclonal antibodies could be manufactured. And Howard Birndorf and Ivor Royston were there.

THE RIGHT PLACE AT THE RIGHT TIME

Howard Birndorf and Ivor Royston don't remember exactly when they met, but they remember where – the labs of the Stanford University School of Medicine. Birndorf recalls that "our lab [Frank Stockdale's] had a collaboration with another guy's lab, a guy named Ron Levy, who was upstairs." Upon arriving at Stanford in 1975, Royston had begun collaborating with Levy, while receiving his clinical training in oncology. Levy was the newest addition to the Stanford medical school faculty at the time (he is now the director of the oncology division). He and Royston had joined

---

[38] To this end, Herzenberg eventually gave hybridoma technology to Becton-Dickinson, which became the first U.S. commercial vendor of monoclonal antibodies as reagents in bulk quantities. (In 1980, a company called Celltech was founded in England for the same purpose; initially, the large scale fermentation and purification of immunoglobulin proteins comprised the major part of its business). Herzenberg provided Becton-Dickinson with myelomas and trained company personnel in the art and science of cell fusion. He was convinced that a large market for monoclonals would emerge in biomedical research sooner rather than later and that an industrial enterprise rather than academic organization would naturally be better suited to manufacture and distribute large quantities of antibodies directed against a broad range of antigens.

the oncology staff at the same time. Levy was using antibodies to probe receptors on the surfaces of B and T cells. He was hoping that his investigations would shed light on the causes and molecular character of malignant lymphomas and other tumors of the immune system. This path of research was right up Royston's alley. He had gotten to know B and T cells very well, was looking at cancer cell surfaces, and had identified cross-reactive antigens on lymphocytes and leukocytes.[39] Royston remembers asking for permission and receiving an invitation to get involved in the work of Levy's lab and to conduct experiments there: "I said, 'I'd like to do some experiments in the lab.' And Levy said, 'Yeah, come right in, whenever you have some time, come in and do the experiments.'" So, Royston set up shop in Levy's space. Later, when the project linking the Stockdale and Levy teams commenced, Birndorf started moving back and forth between the two labs, providing technical help for both teams, making himself at home in both places, and letting himself in at night to conduct his own experiments. Birndorf says, "Ivor was in the lab, putzing around himself, and we met. We struck up a friendship." Royston outranked Birndorf in the medical school hierarchy, but they established and enjoyed an informal partnership in the lab. "We were friends," says Royston. "We got along pretty well together."

---

[39] See, for example, I. Royston, R.W. Smith, D.N. Buell, E.S. Huang, and J.S. Pagano, "Autologous human B and T lymphoblastoid cell lines," Nature 251: 745-746, 1974; I. Royston, P.R. Graze, and R.B. Pitts, "Failure of cultured human T-cell lymphoid lines to stimulate in mixed luekocyte culture," Journal of the National Cancer Institute 53: 361-367, 1974; I. Royston, R.B. Pitts, R.W. Smith, and P.R. Graze, "In vitro immunization against cultured B and T lymphoblastoid cell lines," Transplantation Proceedings (supplement) 7: 531-536, 1975; J.W. Parker, C.R. Taylor, P. Pattengale, I. Royston, B.T. Tindle, M.J. Cain, and R.J. Lukes, "A morphological and cytochemical comparison of human-T and B lymphoblastoid cell lines. Light and electron microscopy," Journal of the National Cancer Institute, 60: 59-68, 1978; R.W. Smith and I. Royston, "I: Human lymphocytes: Participation of T and B cell in mixed lymphocyte reactions," Transplantation Proceedings (supplement) 7: 63-64, 1975.

Along with others in Levy's lab, Royston was using Klinman's splenic fragment culture technique to make monoclonal antibodies for use as tools in the investigation of lymphomas. Royston remembers inquiring about Levy's research when they were first introduced: "I asked Ron, 'Well, what are you going to work on?' And he said he wanted to work on this method for making what were essentially monoclonal antibodies by a technique called the spleen fragment culture system." Royston adopted it, too. Then, late in 1975, news of hybridoma technology reached Stanford. Royston immediately recognized its significance for the immunological study of cancer:

> I'm working on this system [Klinman's], and then the Köhler and Milstein paper comes out in Nature in 1975, in the fall as I recall. We read it and it looked really interesting, you know, the idea that you could fuse these cells and make hybridomas and then those cell lines would grow and be immortal and continually make antibody. It was obviously the answer. I can remember saying, 'Well, that does away with our spleen fragment system.'

Before he could start employing hybridoma technology to make monoclonals, however, Royston had first to obtain some of Milstein's myeloma cells. He states it simply: "I needed that cell line." It did not become available until the spring of 1977, when Leonard Herzenberg returned to Stanford from Cambridge. Royston then had access to the cells by virtue of previous accommodations that he had made with Ron Levy. While working at the NIH, Royston had accumulated a number of different cell lines to use in his research. When he left his post in Washington, he took these cell lines with him, although, technically, they still belonged to the federal government: "I got the government to agree," he says, "that the cells were discarded property, or something like that. I forget the jargon, I forget the word for deactivating something,

but they knew about it. It was just no longer needed by the government." When he accepted his post-doctoral position at Stanford, Royston shipped the liquid nitrogen tank in which the cells were stored, in suspended animation at minus 180 degrees centigrade, to Palo Alto, but he had no laboratory affiliation, and so, no place to keep it. He contacted Levy about the problem: "I said to Ron Levy, 'Look, you're working in immunology and cancer, and that's what I want to do. I've got all these cells. Someday I'm going to need them. Right now, I need to store them. If you will store them for me, you can use them. Here's my liquid nitrogen tank." Levy examined the contents of the tank and found several cell lines valued by immunologists and cell biologists. He recognized that they could be useful in his own work, so he agreed to become the custodian of Royston's property. In return for access to Royston's cells, Levy would add liquid nitrogen to the container as needed.

Through 1976, Royston continued to use Klinman's splenic fragment culture system to make monoclonals, as did others in the Levy lab.[40] Then, in 1977, Herzenberg made his way back to Palo Alto from England. He brought the immortalizing myeloma cell line with him. According to Royston, "Ron Levy asked him for it, and he gave it to Ron." When Milstein's myelomas surfaced in Levy's laboratory, Royston saw that his opportunity had arrived. He suggested to Birndorf that they become personally acquainted, together, with the practice of hybridoma technology: "Howard, you know, we ought to try to figure out how to do this." Royston wanted to make monoclonal antibodies against cancer cells. Considering

[40] L.A. Lampson, I. Royston, and R. Levy, "Homogenous antibodies against human cell surface Antigens. I. The mouse spleen fragment culture response to T and B cell lines derived from the same individual," Journal of Supramolecular Structure 6, 1977: 441-448.

possible applications of the technology, he recognized that monoclonals could perhaps be used to derive knowledge of the structures and functions of cancer cells in ways that polyclonal mixtures could not. (Later, it also occurred to him – and others – that it might be possible to develop monoclonal-based treatments for cancers. Royston imagined that 'exquisitely' specific monoclonals could be used to target and perhaps attack tumors, while ignoring and sparing healthy tissues. He then began to wonder whether hybridoma technology could be refined into a method for selecting particularly potent anti-cancer antibodies and manufacturing them in the quantities required for therapeutic administration in the clinic).[41] Royston asked Levy if he could take clones from the myeloma line on which to experiment. The request was not unusual. The two physicians were colleagues working in the same laboratory, and, inside the lab, cells moved around freely. Moreover, Levy and Royston had already established a cell-sharing precedent. So, Levy gave his blessing. Royston got the myelomas and put them in his liquid nitrogen storage tank.

As news of hybridoma technology began to circulate through the hallways of the medical school, Birndorf, following Royston's prompt and his own natural curiosity, pursued a bit of informal training in the art. Birndorf's recollections of the time are similar to Royston's. He says: "This guy, Len Herzenberg, had gone to Milstein's lab in the UK, and had done a sabbatical there. And he learned the

---

[41] The first therapeutic monoclonal antibody, called Orthoclone OKT3, was manufactured by the Ortho Pharmaceutical Corp. of Raritan, N.J. In 1986, the FDA approved it to fight kidney transplant rejections. The product prevented host T cells from attacking donor kidney cells. The first monoclonal-based treatment for cancer, called Rituxan, was developed by Idec Pharmaceuticals in San Diego and approved for marketing by the FDA in 1997. The company was founded in 1986 by Ivor Royston, Howard Birndorf, and Ron Levy.

technique. And he came back, and I went and learned how to do this from one of his people." From then on, Birndorf became Royston's designated hybridoma maker: "I was the technical guy. Ivor knew how to think about monoclonals – 'What could you do with them? What ones did you want, and why did you want them? I knew how to make them." Royston and Birndorf began experimenting together with hybridoma technology. Birndorf found the work exciting:

> I was pretty stimulated. I was reading journals. I was trying to keep up with Ivor. I mean, Ivor's a pretty bright guy, and I was trying, intellectually, to get into this. I think I did to a certain extent. It was in planning and designing experiments that I didn't have the full breadth and scope, in my opinion, now. I'm not saying I couldn't have done it, but....

But Birndorf had not put years of intensive effort into the study of immunology, as Royston had. Still, Royston recognized Birndorf's talents – his technical capabilities, in particular, but also his general aptitude for scientific work and his zeal: "Howard was a master's degree person, as I recall, but he always was able to, and he always wanted to do more than that." Royston's theoretical and clinical interest in hybridoma technology put him on a new professional trajectory, while Birndorf's enthusiasm and his practical skill in the art made him a valued collaborator. Although they didn't know it at the time, the pair had lucked into a gold mine, and their experience in biomedical research had prepared both of them to take advantage of it.

For Royston and Birndorf, the oncology division of the Stanford University School of Medicine was the right place and the spring of 1977 was the right time. It was made so by Herzenberg's return to Palo Alto from Cambridge with cells from

Milstein's P3-X63Ag8 myeloma line and the know-how required to make hybridomas and monoclonals. Thanks to Herzenberg, the Stanford University School of Medicine was, in 1977, one of the few places on the planet where hybridoma technology could be learned and practiced. Cambrosio and Keating list the following groups as early recipients of Milstein's cells: "Klaus Rajewsky's team at the University of Cologne; Hilary Koprowski's team at Wistar Institute; Norman Klinman and Roger Kennett at the University of Pennsylvania, who had received the myeloma cell line from the nearby Koprowski with Milstein's agreement; Herzenberg's group at Stanford; and a group of French researchers associated with Gérard Buttin and Pierre-André Cazenave."[42] The people working in these groups knew of each other; many were personally acquainted, and some had established cooperative professional relationships. They constituted an 'invisible college,' a network of loosely connected researchers devoting their energies to the same problems and communicating about them. When Royston and Birndorf obtained myeloma clones from Levy and began playing around with them in the lab, they entered select company – they found themselves contributing, along with thought leaders in the fields of immunology and cell biology, to the development of an important emerging technology. Birndorf remembers: "I was working with Ivor, and Ron Levy, and Frank. We were all doing this stuff, and I was one of the people who knew how to do it then."

DOWN TO SAN DIEGO

Just as Royston and Birndorf began to dabble in hybridoma technology, Royston's two-year postdoctoral fellowship was drawing to a close. There were no

---

[42] Cambrosio and Keating, Exquisite Specificity, p. 93.

open positions in oncology at Stanford – Ron Levy had snared the last one – so, through the 1976-1977 academic year, Royston had been looking around for a permanent post somewhere. He was positioned to move laterally from Stanford, so to speak, to an institution that offered affiliates both high prestige and opportunities to do first rate medical science. He had finished all of his training, and had established an impressive record as an independent researcher. He was still running on a very fast track. And although he was up against the very best horses, he still expected to finish in the money. Royston applied for positions at several places, including the School of Medicine at the University of California, San Diego. He found the UCSD opportunity particularly appealing because the university was planning to open a new cancer center in the city and the duties of the open position would include both research and clinical practice.

Royston informed Birndorf that he had applied for the San Diego job. He suggested that, if he were offered the position and accepted it, Birndorf might make the move with him as his chief technician. Birndorf recalls receiving the invitation: "One day, he came to me and asked, 'How would you like to come with me to San Diego, to set up and run my lab?' And I said, 'Yeah, that sounds pretty good." Birndorf was ready once more for a change of scenery: "I really didn't like Palo Alto all that much. It was very sterile, you know. If you had a nice house and everything, it might have been OK, but as a student, if you will, it wasn't so great." Royston wanted to bring Birndorf with him because Birndorf was now a skilled monoclonal-maker, one of just a handful in the world: "He had learned the techniques with the monoclonal antibodies. He was very interested in working in this area. I thought he

would help jump-start my program by not having to look for somebody new, especially in this new area. I would be able to bring somebody who had some experience in this area." Royston was scheduled to travel to San Diego for an interview. When the time came, Birndorf, who had never been to the city, accompanied him. Royston says, "I brought him so he could see San Diego. He didn't know San Diego." Birndorf liked what he saw. He especially liked the beaches and the relative warmth of the ocean some three hundred and fifty miles south of the Golden Gate: "I'd just taken scuba diving lessons up in the Bay Area. I'd had my check-out dive earlier that year." Characteristically, Birndorf thought first about what he might do for fun in San Diego. As it happens, the scuba diving is excellent in the waters along the Southern California coast. At the time, it didn't take much more to persuade Birndorf to pull up his tent stakes.

On their visit to San Diego, the pair stayed at the home of one of Birndorf's oldest friends, a high school chum from Michigan. They slept on the floor of his living room. At the university, Royston was interviewed by physician and cancer researcher John Mendelsohn. Mendelsohn was a Texan who had taken a position at UCSD as an assistant professor in 1970. By 1977, he was a rising star, well on his way to a full professorship. He later moved on to positions of leadership at New York's Memorial Sloan-Kettering Cancer Center and Houston's MD Anderson Cancer Center, which he still directs. When Royston first spoke to him, Mendelsohn was involved in establishing and funding the new UCSD Cancer Center. Royston told him about monoclonal antibodies and his plans for a research program. Mendelsohn was excited about Royston's ideas and offered him a job as an assistant professor of

medicine.[43] Royston was also weighing offers from several other institutions. He gave serious consideration to one he had received from the medical school at Emory University in Atlanta. Had Royston decided then to go to Atlanta to conduct his research, the industrial development of biotechnologies in San Diego might have followed a very different path. Hybritech gave San Diego a head start in commercial biotechnology. Without it, the San Diego industry might not have established its position of leadership in the field. And the bioscience industry in Atlanta might have developed in a very different manner, as well. With a little luck, Georgia might have benefited from an early boost into the hybridoma business rather than California (or maybe not).[44] In the end, though, Royston opted for UCSD, primarily because of the new cancer program that Mendelsohn was organizing. Within it, Royston was appointed to the department of clinical immunology. His office was to be located at the UCSD Medical Center in the Hillcrest section of town, near the city center. He

---

[43] Mendelsohn soon began using monoclonal antibodies in his own research on cell growth factors and receptors. See, for example, T.K. Kawamoto, J.D. Sato, A., Le, J. Polikoff, , G.H. Sato, and J. Mendelsohn,, "Growth stimulation of A431 cells by epidermal growth factor: Identification of high-affinity receptors for epidermal growth factor by an anti-receptor monoclonal antibody," Proceedings of the National Academy of Science, 1983, 80: 1337-1341.

[44] It is impossible to say what might have happened. In any case, government, business, and academic leaders in Atlanta are now making a concerted effort to encourage the formation of new life science companies in the city and to support their growth. They have experienced some success. According to Ernst & Young, the city now ranks ninth in the country as a center for biotech development. See Michael S. Hildreth, Scott Morrison, Ron Budd, Chris Nolet, Resilience: Americas Biotechnology Report, 2003, Ernst & Young, LLP, 2003. Touting the research base in the city's numerous academic institutions from which commercial firms can draw ideas and personnel, the web site of a local booster organization – the Metro Atlanta Bioscience Council (http://www.atlantabioscience.com) – proclaims that "Atlanta is smarter than other cities." Maybe the city has put together a smart plan for future economic and technological development – time will tell – but while much important scientific and medical research is presently being conducted in Atlanta and its suburban areas, the scale of bioindustrial activity in the state of Georgia does not begin to match that found in places like California and Massachusetts.

was also assigned laboratory space at the Veteran's Administration Hospital near the main university campus several miles to the north in La Jolla.

Together, Royston, the astute careerist, dedicated physician, and cancer warrior, and Birndorf, the vagabond hippie, scuba diver, and 'golden-handed' experimentalist, readied themselves for a departure from Stanford. In order to commence with his planned monoclonal antibody research in San Diego, Royston had to transport the myeloma cells to his new laboratory. Today, cell lines and other biological materials are not moved freely by individuals across organizational boundaries because it is generally recognized that they may be of significant economic value to academic institutions and commercial firms. Movements of scientific properties are now closely monitored, documented, and governed by material transfer agreements.[45] In the 1970s, however, when the biotechnology industry was in its infancy and academic researchers and administrators were not yet accustomed to privatizing research and materials, there were no such provisions in place, except for cases involving hazardous substances. Royston recalls that, at the end of June in 1977, when it was time for him to move from Stanford to San Diego: "I basically just took the cells with me." He arranged for Ron Levy to ship the liquid nitrogen tank containing the myelomas to his new lab at the La Jolla VA Hospital.

In May, Birndorf embarked on a second trip to San Diego to rent living quarters. He found a place to his liking in the tiny beach town of Leucadia, several miles north of the La Jolla campus. He took half of an A-frame near the beach and the

---

[45] See Michael A. Gollin, "Biological Materials Transfer Agreements," Bio/Technology, 1995, 13: 243-244.

water, not far from Neptune Avenue, the cliff road in Leucadia. By the end of June, when it was time for him to leave Palo Alto to move down to Southern California for good, he had no transportation. He had wrecked his last automobile and he hadn't replaced it. So, he bought a green Chevy Vega for five hundred dollars. "And," he adds, "it was a really ugly green." Birndorf packed his dog and his suitcase into the Vega and headed south down Interstate 5. The rest of his belongings were loaded into a truck that Royston had hired. They didn't take up much room. "My possessions were meager," Birndorf says, "I had very little stuff." I-5 stretches the entire length of California, from Oregon to the Mexican border. Drivers heading south from the Bay Area to San Diego find monotonous landscapes for much of the way, until they approach the Los Angeles area. The road runs straight down the flat, agricultural Central Valley, across an expanse of high desert, and then descends into the San Fernando Valley. At the southern rim of the valley, it hops over the Hollywood Hills, and cuts across the L.A. Basin. After bisecting the city and the suburbs of Orange County, the freeway swings out at San Juan Capistrano to the west and the Pacific Ocean. It then runs along the coast past the San Onofre nuclear plant, through the marine base at Camp Pendleton, and into the small beach city of Oceanside at the northern edge of San Diego County. Birndorf made the trip in July of 1977. He still associates the journey with a major transition in his life:

> I'll always remember that day. I remember that drive through the Central Valley, and how hot it was, stopping to get my dog water at gas stations. I remember getting through L.A., and then coming through Camp Pendleton, and seeing the beach and smelling the salt air, and it was really cool. I really felt like I was off on this fabulous adventure. It was the second time in my life that I'd moved from what I knew to something totally unknown, and it was like I was taking a big risk. I

> wasn't actually, but that's the way I saw it. I just saw it as a big adventure, and I just love that. It's cool. It's just exciting to do something totally different, to go somewhere you don't know, to meet new people, you know, all of that. And that's what I did. It was Fourth of July weekend, so I had a few days off, and then we started to work.

Royston's first laboratory at the La Jolla VA Hospital was tiny, a small room of about 250 square feet up on the sixth floor. It had lab benches lining both sides, and a single bench top tissue culture hood. "And that was it," say Birndorf. "They didn't have any room and Ivor had to take the least attractive space because he was the new kid. We had no equipment, no supplies, so my first job was to start equipping. I immediately made lists out, went and got vendors, bought things, put them in the lab, set up the lab, and then, as soon as I could, I started doing experiments." The lab was funded in part by government grants that Royston had secured. "I had gotten some funded," he says, "because monoclonal antibodies were a brand new, hot area." In addition, the department at the medical school provided some start-up money with which to purchase equipment and supplies and pay assistants. When the lab was adequately tooled (in this instance with things like glassware, tissue culture plates, pipettes, shaker baths, cyto preps, incubators, a centrifuge, a fluorescence microscope, a gamma counter, and so on), Birndorf started making antibodies against cancer cells. Royston elected to study lymphomas, cancers of the lymph system, largely because he had lymphoma cells that he had brought down from Levy's lab at Stanford to use as antigens. Birndorf started immunizing mice against the human cancer cells, removing their spleens, performing fusions with splenocytes and myelomas, and screening, culturing, and harvesting monoclonals, which were then used to differentiate and analyze cancer cells: "We did a lot of fluorescence microscope studies. We made

monoclonals all the time. That was what I was constantly doing – making them and keeping them up." This was groundbreaking work in 1977. Says Royston:

> No one in San Diego had ever worked with monoclonal antibodies. I was the first person to do that. This was just '77 and Köhler and Milstein had just published in late '75. Ron Levy was doing it up at Stanford. There were some people doing it on the East Coast at the Wistar Institute, and some at the Albert Einstein Hospital in Seattle. I could maybe count on one hand the number of places that were doing it. It was a brand new technology. But we were the ones who did it in San Diego.

THE MANY MOTHERS OF INNOVATION

Having garnered sufficient experience with hybridoma techniques at Stanford, Birndorf was able to move the technical part of the work quickly ahead without a hitch. Royston began to generate a lot of information on the characteristics of lymphoma cells: "It worked out quite well. We were making antibodies against these lymphoma cells, and it was very easy for us to do it." It was not long before Royston and Birndorf were struck by the idea of starting a company. They saw that they could perhaps make monoclonal antibodies in order to sell them. In the beginning, the plan was simply to supply researchers with antibodies. Birndorf recalls, "We knew that [monoclonals] might have diagnostic applications. We even knew that they might have therapeutic applications, but our initial idea of a business was not that. It was really, 'Let's make and sell antibodies for research purposes.'" To their knowledge, no one else was doing it. Len Herzenberg had not yet bequeathed hybridoma technology to Becton-Dickinson. None of the large companies selling conventional polyclonal antibody sera had yet begun marketing monoclonals. It was still too early in the game for that. It was still just the first quarter of 1978.

Royston and Birndorf drew the same conclusion about hybridoma technology that Herzenberg had – it could be employed, they saw, as a means of producing standardized reagents. They knew from experience the limitations associated with polyclonal antibody sera. Says Birndorf: "We used to buy a lot of these research antibodies. That was the thing that really stimulated this. We'd buy them and each batch was different, and they had different immunoreactivity, and we said, 'Shit, we could improve upon this with monoclonals.'" Polyclonal sera are purified from the blood of immunized animals. Each mixture contains many different antibodies that target many different antigenic determinants – different binding sites on the antigen against which the animal was immunized (and sometimes on other antigens, as well). The composition of every mixture is different, and every drop of serum is different than the next. With hybridoma technology, however, it would be possible to produce large amounts of genotypically identical immunoglobulins, the problems of heterogeneity and variability in polyclonal mixtures would be eliminated, and antibody supplies could be continuously replenished without having to purify blood, and without having to immunize and bleed animals repeatedly. And the hybridoma method was cheaper, to boot. As Royston talked to suppliers of conventional research antibodies about hybridoma technology, he began to realize just how far out on the curve he and Birndorf had landed:

> They would say, 'Well, we have all these farms with goats and sheep. What are we going to do with them?' We would do away with all that. It was a major paradigm shift. You don't need goats and sheep and horses to make monoclonal antibodies. What you need is some incubators and some flasks, and maybe some bottles, or maybe a fermenter device, to grow cells. And I realized that this was a major paradigm shift in thinking.

Royston and Birndorf figured that once word of hybridoma technology and the availability of standardized, highly specific antibodies spread, a fair-sized market for monoclonals would develop among scientific and medical researchers. And they saw that nobody was yet positioned to take advantage of it. This was an opportunity. Neither of them is quite sure who first suggested the idea of starting a business. Both now agree that they came up with it together. They describe it as the outcome of a collaborative process, something that emerged over time from numerous idle conversations. Apparently, at some point in discussions about the practice and problems of making large batches of antibody for use in scientific and medical experimentation, one of them said, 'Let's just start our own business.' That the pair entertained and seriously pursued this idea, which was mostly foreign to the culture of the life sciences at the time, can perhaps be attributed to their earlier experience up in the Bay Area. The Bay Area was the birthplace of the biotech industry. A venture capitalist's office in downtown San Francisco, a UCSF laboratory, and, a bit later, a warehouse in South San Francisco, were the sites of the world's first biotechnology company, Genentech.[46] The Stanford University campus was no more than twenty miles down the road from South San Francisco, and Royston and Birndorf were in residence on it when the new firm became operational.

For life scientists, the Bay Area in the mid-1970s was, as Royston says, a place in which "things were really happening." Things were happening scientifically, and

[46] The first, that is, if the term 'biotechnology' is defined as the practical application of tools derived from late advances in molecular biology, genetics, and biochemistry, or from the new 'biological' approach to immunology.

they soon began happening commercially and industrially, as well. Genentech was founded by Herbert Boyer in 1976, after he and Stanley Cohen had demonstrated the feasibility of gene cloning and splicing – the fabrication of recombinant DNA – three years earlier. Royston knew about it: "I was cognizant of Cohen and Boyer and recombinant DNA. And Cohen was right there [at Stanford]. I went to his lab to talk to him."[47] He learned of Genentech, too (although, at the time, it was just a tiny start-up, just an academic lab, a handful of itinerant post-docs relocated to a nondescript industrial park – an obscure dark horse in a race with UC and Harvard big shots to clone a human gene).[48] Even closer to home was another example. "I remember this guy," says Birndorf, "named John Daniels. He was trying to start a company that ended up being Collagen, Inc." Daniels was a faculty member in oncology at Stanford. He developed a method of modifying donor collagen for use in xenotransplantation by identifying and removing certain immunogenic materials. The company was eventually successful and is still in business. It manufactures injectable collagen-like substances for cosmetic procedures. Royston and Birndorf had each met Daniels and were aware of the company that he was putting together. They learned that it was possible for scientists to start companies, that such activities were not

[47] Stanley Cohen never attempted to commercialize his invention and elected not to become involved with or accept a personal stake in Genentech when Boyer founded the company. Bertram Rowland, the attorney who wrote and filed the recombinant DNA patent on behalf of Stanford University, tells of a conversation with Cohen that illustrates the scientist's attitude of indifference toward the proprietary status of his work: "Cohen insisted that the invention had no commercial application, was not patentable, and was really only a minor extension of what had been performed by others. However, he agreed to be a good academic citizen and cooperate if Boyer would go along with the filing." See "Bertram Rowland and Cohen/Boyer Cloning Patent," http://www.law.gwu.edu/tech/rowland.asp.

[48] The Genentech story is told in Stephen Hall, Invisible Frontiers: The Race to Synthesize a Human Gene, New York: Atlantic Monthly Press, 1987.

formally prohibited by institutional rules, and that certain kinds of academic biological research now perhaps had some value in the marketplace.

Still, by their own accounts, when Royston and Birndorf came across hybridoma technology, they weren't thinking about commercialization and profits. During their time at Stanford, they were fully engrossed in their scientific work, in learning how to use monoclonal antibodies in the laboratory. They weren't sniffing around for business opportunities: "We weren't talking about starting companies of anything like that," says Birndorf, "we were just talking about science, and what kind of neat things you could do with this technology in terms of answering some question for science." It was not as if, by starting a company, Royston and Birndorf decided to jump on the biotech bandwagon. At that point in time, there was no such bandwagon. Prior to the mid-1970s, commercializing research and becoming directly involved in private business ventures were things that bioscientists did only occasionally. Even rarer were instances in which biologists or medical researchers became entrepreneurs and started new businesses of their own. Nevertheless, when it later came time for Royston and Birndorf, two academics, to consider seriously becoming entrepreneurs and founding a new commercial entity in San Diego, they knew that others had done the same thing in the Bay Area. Royston recalls: "I was familiar with Collagen and Genentech. So, I knew it was doable."

Royston's experience was unusual. In the 1970s, disdain was the attitude maintained by many 'high-minded' academic bioscientists toward industrial research. Researchers commonly demeaned industrial (or 'applied') science as the province of second-raters – hacks lacking the insight, creativity, or spark required for 'pure'

scientific inquiry. Only after some big name scientists hitched their wagons to new biotech companies did this common prejudice begin to evaporate. By the middle of the next decade, biologists generally agreed, as the following statement by an unnamed researcher indicates, that industrial science could be respectable; it could be challenging and first-rate: "Nowadays it is understood if someone like Gilbert [Walter Gilbert, a Nobel prize winning scientist] quits Harvard [for industry]. Being in a company does not imply mediocrity."[49] Before the biotech 'revolution' and the institutional and organizational changes that characterized it, however, this was not the case – being in a company did imply mediocrity. Until biotech firms began to crop up around certain major scientific institutions in the late 1970s and early 1980s, the term 'industrial biology' was nearly synonymous with fermentation, while fundamental advances in the life sciences were made almost exclusively in academic settings. Biologists roundly assumed – they knew – that industrial labs were not on the cutting edge; industrial scientists did not discover, they merely applied, and little scientific honor or glory could be expected from that. With the examples of Genentech and Collagen, though, Royston and Birndorf were exposed to a different set of facts. Consequently, neither of them worried about being stigmatized by association with the hoi polloi.

Other aspersions cast by academics on the participation of life science colleagues in industry expressed deeper concerns regarding professional ethics and institutional integrity. Both before and after biotech companies became known for

---

[49] Quoted in Henry Etzkowitz, "Entrepreneurial Science in the Academy: A Case of the Transformation of Norms," Social Problems 1989, 36, 1: 14-29; quote on p. 22.

scientific work of 'recognized quality,' some critics of commercialization grounded contempt for business and the worldly pursuit of profit, not in the alleged inferiority of science conducted in industrial labs, but more broadly and more explicitly in ideological rationales. Some objected, as some still do, to science in the service of capital.[50] The 'purists' were convinced that the privatization of knowledge was antithetical to science and threatened to corrupt the enterprise. They contended that the entanglement of academic researchers in commercial ventures created, unavoidably, conflicts of interest and commitment that would disrupt scientific institutions and impede scientific progress.[51] Looking backwards from 1985, Robert Rosenweig drew the political line dividing scientific entrepreneurs and academic traditionalists in this manner:

> When, in the mid-1970s, it became clear that important economic stakes might suddenly be at issue in the conduct of what had hitherto been the most fundamental biology, some members of that scientific community moved vigorously to exploit the new potential. Others, however, equally distinguished and equally serious-minded worried that the introduction of commercial considerations, especially the

---

[50] See David Noble, "The Selling of the University," The Nation, February 6, 1982: 1, 143-148, and more recently, Sheldon Krimsky, Science in the Public Interest: Has the Lure of Profits Corrupted Biomedical Research?, Lanham, MD: Rowman & Littlefield, 2003. The concluding chapter of this dissertation includes a thorough treatment of these issues from a sociological point of view. Occasionally, scientists' objections to mixing science and business are associated with a principled dislike for capitalism. Scientists are a left-leaning group, by and large. A recent survey of U.S. and U.K. readers of The Scientist found that 10% of respondents (344 in all) identified themselves as socialists. Forty-four percent claimed to hold liberal views, while just 14% said they were conservative. Four percent identified themselves as libertarians. The remaining responses (22%) were "unclassifiable." See "Political Scientists: Politics, Like Science, Generates a Whole Lot of Opinions," The Scientist, 2003, 17, 10: 10.

[51] Henry Etzkowitz, "Entrepreneurial Science in the Academy: A Case of the Transformation of Norms," Social Problems 1989, 36, 1: 14-29. Etzkowitz suggests that larger institutional forces – the decline of public funding for basic scientific inquiry in the 1980s, for instance – were responsible for changing values and norms in the sciences and more receptive attitudes of scientists toward participation in industry.

> pressure to protect patent positions, would damage the fabric of their science.[52]

Ivor Royston was among the original members of the first group. He wasn't averse to the idea of privatizing research and making money from scientific endeavors. Although negative attitudes regarding the commercialization of science were common among his colleagues, and although business and bioscience were, in fact, two very distinct spheres of social life when he moved to San Diego, he wasn't put off or intimidated by the idea of starting his own company. Business activity did not lie entirely outside his personal comfort zone; he had some previous experience on which to draw. In 1960, at Calvin Coolidge High School in Washington, D.C., the father of one of Royston's classmates, the president of a bank, decided to give his son and his school friends a practical education in business and finance. He helped to organize an investment club at the school. Royston was invited to join. The group adopted the name 'The Chessmen' because there were sixteen among them. The students assembled an investment portfolio. They started by purchasing second mortgages at a discount:

> We would look in the newspaper for second trust mortgages that were for sale. Then, someone would go out and look at the house and give a report to the group, and say, you know, 'this is a really good home, well-built, and these people have been paying their mortgage on time for the past ten years and it's really very safe,' and so on and so forth, and we would actually go ahead and invest in these mortgages. I put my allowance money in there, and I got my father to provide some money for me. I basically invested my money, whatever my savings were. Over the next two or three years, our investments did go up significantly. We actually started making money and it was doing quite well.

---

[52] Robert M. Rosenweig, "Research as Intellectual Property: Influences Within the University," Science, Tehcnology & Human Values 1985, 10, 2: 41-48; quote on p. 48.

The Chessmen did well enough to receive a write-up, a full-page article, in the Washington Post, in 1963. Royston still has the wrinkled paper. In the end, however, the students' reach exceeded their grasp – they decided to take a limited partnership in a major high-rise development project that did not do well. The developer ran into financial difficulties and the Chessmen lost all of their money. Nevertheless, Royston recalls that participating in the club "was a lot of fun." He was fascinated by science, but he had enjoyed learning about business and finance, too. Royston was also exposed to business in a practical way through his association with his first father-in-law, a very successful real estate developer. His father-in-law owned office buildings in downtown Philadelphia and was involved in various other real estate deals in the U.S. and Europe. Royston had the opportunity to observe him closely, and to become familiar with his modus operandi. And from him, Royston received informal instruction on strategic thinking in business. The young scientist was tutored by a master. Of his father-in-law, Royston says:

> He had a net worth of many millions of dollars, and he was also very, very quick, very intelligent, a very high intellect person when it came to mathematics and business things. He was constantly trying to challenge me to solve business problems and things like that, and if I didn't do well at it, he'd tell me how stupid I was. He was a pretty arrogant guy. I don't know how much of a positive influence he was on me in terms of getting involved with business people, but I certainly wasn't afraid to get involved with them because, if I could deal with him, I could deal with anybody. Through that six years of experience of him being my father-in-law, I had the opportunity to relate to a successful businessman, and to see some of the positives, and some of the negatives. I saw how he treated certain people in business and I didn't appreciate it, I didn't like it. I think, though, that through these associations, I sort of just naturally learned, and a lot of things in business just came easily. I understood it. I mean, I wasn't afraid of business. It seemed to be part of my life.

As Royston tells it, though, his decision to go into business did not express any special ambition to conquer a new domain, to achieve success for its own sake in a new pursuit. He was not driven in any powerful way by a passion for business. He didn't really have an appetite for wealth or prestige derived from success in business. To the contrary, he remained firmly committed to medical science and his personal war against cancer. Royston recalls that the idea of commercializing hybridoma technology was connected to his wish to generate for scientific and medical purposes more antibodies than the tiny laboratory at the VA Hospital was equipped to produce. He envisioned himself conducting tests of monoclonal-based cancer therapies. He was planning to inject antibodies into patients with lymphoma and leukemia. In theory, they would seek out tumors of the lymph system and cancerous cells in the blood, and perhaps attack them, either by interfering in some way with cell growth, or by delivering chemotherapeutic agents to cell surfaces. He was concerned with making enough antibodies to administer test doses to large numbers of patient volunteers in experimental clinical trials at the cancer center downtown:

> I can remember thinking, 'OK, I can see now that we can make antibodies, and we can probably make antibodies that react with cancer cells and not normal cells, or more preferentially with cancer cells – how am I ever going to be able to treat patients? That's where the idea of the company came from – how was I going to be able to manufacture these antibodies? We couldn't do it at the university. We needed big vats and fermenters, and whatever it was that we needed – lots of mice. There's a technique for making antibodies by injecting them into the peritoneal cavity of the mice and getting fluid. But I realized that we were going to be encumbered by not being able to have manufacturing.[53]

[53] The mice would be needed for the large-scale production of monoclonal antibodies – the manufacture of immunoglobulins by the gram. Monoclonals could be harvested from the supernatant medium containing hybridomas in tissue culture well-plates, but hybridomas injected into the abdominal cavities

Apparently, at that juncture in his career, Royston was concerned more with advancing his scientific and medical research than he was with achieving success in business. Starting a company happened to fit in with his plans. It promised to contribute to the accomplishment of his scientific and medical goals. "At no point," says Royston, "was I thinking that I was going to make a lot of money or build some major industry. I just wanted to manufacture some antibodies. I was excited because it was something brand new, and there was the possibility that this could help me with my research developing new ways to treat cancer." In fact, in the plans that he formulated with Birndorf, the company was to be primarily Birndorf's responsibility. Royston had no intention of giving up his UCSD appointments. He conceived of his participation in the business as a sideline: "I would become basically, the acting scientific director, and do it in my spare time. You know, I was an assistant member of the faculty. I wanted to be tenured someday." Birndorf corroborates Royston's account: "We were looking at it like we could start a little business, Ivor would own a small amount, and I would be the major business person because Ivor wasn't going to leave the university. He would own a portion and I would work it."

Birndorf welcomed the idea of leaving the university for a private firm. He didn't balk or hesitate for a moment. He had no ethical misgivings. Despite the length of his hair and the full beard that he wore at the time, which might have been

---

of mice can rapidly multiply and grow successfully in these environments as tumors. As they grow, the amounts of antibody that they secrete into peritoneal fluids increase exponentially. The fluids can then be extracted and purified to yield antibodies in high volumes. Hybritech employed this method for several years until refinements in bioprocessing techniques made the culturing of myelomas and the harvesting of monoclonals in fermentation tanks more reliable and cost effective.

read as signs of a hippie's relative indifference toward material concerns, Birndorf didn't have anything against doing some business and making some money. In fact, looking back, he believes that he was just waiting for a chance. He now considers himself a natural entrepreneur. "I was fortunate enough," he says, "to get into a situation where I could exercise my genetic traits."[54] Whether due or not to some natural aptitude or predisposition, when an opportunity had beckoned once before to derive financial gain from scientific work, Birndorf had taken a stab at it. While employed at the Michigan Cancer Foundation in Michigan, he had attempted to license an invention of sorts that he had made. He was working in the foundation's laboratory with instrumentation manufactured by a company called Bio-Rad. He was using the equipment in a novel way, as part of a method for purifying the viruses with which he was experimenting. He needed to separate the viruses from certain elements of the soups that contained them, and he managed to fashion a workable isoelectric focusing method – a technique for separating proteins by electric charge – using the BioRad tools at his disposal. Birndorf called the company and told them about his novel system. The firm sent a representative to visit Detroit. The emissary bought him a dinner and listened to his presentation, but nothing ever came of it: "This was like my first science/business thing," Birndorf recollects. "They never called me back. I was actually pretty disappointed." No further opportunity presented itself until Birndorf acquired hybridoma technology, which turned out to be a very valuable piece of intellectual property. People called back about hybridomas.

---

[54] Andrea Moser, "Biotech's Johnny Appleseed: How a Hot Shot Entrepreneur Evaluates His Wanna-Be Employees," San Diego Metropolitan, October 1997.

Unlike Royston, Birndorf's interest in the idea of starting a company had to do primarily with the possibility of financial gain. He doesn't mention the production of monoclonal antibodies for Royston's cancer research as an incentive. Birndorf's outlook was different than that of his partner because his circumstances were different. Royston was dedicated to his job at the university; Birndorf was not. He had no great stake in UCSD, and little reason to display loyalty to the institution. The university had made only a minimal commitment to him personally – it permitted the medical school to hire him as a laboratory technician. Birndorf was promised nothing more than a modest paycheck, as long as he showed up to punch the clock. The job was taking him nowhere, and he was beginning to worry a bit about his future. When loose talk about going into business took on some gravity, Birndorf found himself powerfully motivated by the opportunity to make some decent money, finally, with his laboratory skills. He hoped that the project would provide him with a comfortable income and maybe even a career of some kind, as well. So, according to Birndorf, the idea of a company came to fruition, in part, because of pressure that he exerted on Royston – an expression of dissatisfaction with his circumstances:

> I was getting upset about my income. I kept pushing Ivor about my income. He kept trying to get me more money. And he was trying, as hard as he could. He was paying me some overtime. I think my salary was $14,000 and, with overtime, I was making about $16,000. You know, I wanted a better car, I wanted something. By then, I was twenty-seven years old. I was really starting to wonder 'What the hell am I going to do with myself?' I was in a dead-end job. I'd reached the highest level of research associate. There was nowhere I could go without a Ph.D. Either I had to go back to school – which was one thing I was really considering, to get a Ph.D. in science – or change careers, or do something. We hired several more people in the lab. I was in charge of them, which gave me added responsibility, so Ivor could pay me a little bit more, but he was totally bound by the

> university. There were salary ranges, and so, there was only so much he could do, given the situation. And I think part of the reason that we came to do this whole thing was my pushing, saying, 'Hey, I need more money. You know, I can't keep doing this.'

CONTINGENCIES

According to Birndorf, the idea of starting a company emerged from the particular set of circumstances in which he and Royston happened to find themselves. They had chanced upon a valuable technology that was ready to be exploited commercially. They were both intelligent, both had backgrounds that prepared them to do something with the technology, and, together, they possessed at least some of the skills required for establishing a new technology-based firm. Finally, they both had reasons for undertaking a private entrepreneurial venture. One wanted to cure cancer; the other wanted to make a living. Royston wanted the capacity to manufacture antibodies for clinical trials; Birndorf wanted to be able to take care of himself, because the institution with which he was affiliated displayed no special interest in his personal welfare. Each turned over the notion of entrepreneurship in his mind, and each decided that starting a business could serve his purposes. Birndorf believes that his urging provided the main impetus. He says, "I don't think it was Ivor's idea, and I don't think it was my idea. I think it was joint. It just sort of evolved, and I do believe, in retrospect, that part of that evolution was me always pushing, always thinking about how I could make more money, you know, saying, 'Ivor, I can't live like this, I need more money.'"

Royston and Birndorf's entry into the ranks of entrepreneurs was situational. Had their situations been different, it is likely that their actions would have been

different, too. Birndorf remembers that before Royston was introduced to hybridoma technology and new possibilities for cancer therapy, and before he was exposed to constant griping from his assistant regarding pay, his boss was a narrowly focused doctor and medical researcher, and perfectly satisfied with that life. "Ivor's clearly an entrepreneur," says Birndorf, "no question about it – but he hadn't been to that point." Only within a definite set of propitious circumstances did Royston's entrepreneurial talents emerge and display themselves. The same was true for Birndorf. A business partner would later say, "Howard is one of the most entrepreneurial guys I've known. If his mother hadn't wanted him to be a doctor, he'd be running most of Detroit today, probably the construction industry in Detroit."[55] Perhaps, but perhaps not. Before the chance to start a company presented itself, Birndorf had not been actively pursuing or searching for business opportunities. He seized the chance when it came, but, without it, he might well have followed some other path. Fortune had to smile before Howard Birndorf became an "entrepreneurial guy."

Entrepreneurs become entrepreneurial when the time and place are right. Hybritech's future founders were lucky to be present together at the Stanford University School of Medicine in 1977, when that time and place became the right one for the San Diego biotechnology industry – although, at that point, of course, there was no such industry in San Diego and no reason to anticipate one. There was no way for anyone on the scene to know that such a chance was in the making. Before César Milstein's myeloma cells and Georges Köhler's hybridoma-making skills were transported by courier from England to Palo Alto, Stanford wasn't yet the right place

[55] "Meet the Entrepreneur," UCSD CONNECT video, May 1991.

and time. After the cells and the technology had each taken up residence in the medical school laboratories, however, the stage was set. Herzenberg's return to Stanford initiated a cascade of events that culminated with the founding of Hybritech and the biotechnology industry in San Diego. Of course, Royston and Birndorf both had to be up for the task. They had to be ready and able, and they were. Royston knew what to do with monoclonal antibodies when they landed in his lap. In a sense, he had been preparing for the opportunity his entire life. Birndorf's prior experience in cancer research had readied him, too, to play the role that chance and history had written for him. So, Royston and Birndorf were the right individuals, but many other immunologists and technicians had been similarly prepared. Royston and Birndorf just happened to find themselves in the right part of the country, the right building, the right department, and the right laboratories, among the right people. Unlike all the rest, they just happened to be the right individuals in the right place at the right time.

VII. HOW TO START YOUR OWN BUSINESS

He who has a thousand friends has not a friend to spare.

Ali ibn-Abi-Talib

"IT'S WHO YOU'VE DATED, YOU KNOW?"

Having decided to try to create and run a company of their own, Royston and Birndorf had to start thinking about how they would finance it. The first step in establishing an industrial operation was clear. They would need to set up a laboratory in which to grow hybridomas and screen and harvest monoclonal antibodies. Birndorf knew how to do that. He had just finished outfitting Royston's UCSD lab a few months earlier. But money was available for that project – Royston's grants and university funds had underwritten it. Raising funds for a private venture was a different proposition, and neither Royston nor Birndorf had a clear idea about where to begin. They had heard of Genentech and Collagen, but these were just tiny companies at inception. Neither made an earth-shaking impact when founded. Royston and Birndorf were aware of them, but not overly impressed, and, at the time, they were too wrapped up in matters scientific to inquire about financing details. Venture capitalists had seeded these firms, but venture capital wasn't yet a household word in 1978. Royston and Birndorf didn't know about the venture capital business. What they knew with certainty was that they couldn't finance the proposed venture themselves. Birndorf recalls: "We didn't know where we were going to get the money, because I didn't have any money, and Ivor didn't really have any either. He had more money than I did, but he really didn't have any extra."

Royston decided to start with the basics. "In my typically compulsive way," he recalls, "I went to the library and got a book called How to Start Your Own Business." He still has the book. He and Birndorf then began to follow the author's recipes for planning a start-up. They must have concluded that wealthy individuals would be a likely source of funds for a company of the sort they were planning, for Birndorf was soon on a plane back to the Midwest, searching for 'angels' within his constellation of acquaintances: "I went back to Detroit and pitched this to several wealthy friends of my parents. I had a friend in Chicago who was a doctor and he had friends who were commodities brokers, and I went and asked if they would be interested." Unfortunately, he found no takers. "This was all so technical and so wild that nobody really understood it. They didn't understand it enough." Birndorf returned empty-handed and frustrated, but while he was away from San Diego trying to sell the idea, Royston had spoken to his wife, Colette, an oncology nurse whom he had recently wed. He explained to her what he and Birndorf had in mind. The conversation led to a serendipitous connection that, as Royston says, "really moved things along." His wife mentioned to him that she had once dated a young man in the Bay Area named Brook Byers, who was involved in venture capital. She told Royston, "'He said he starts companies. Why don't I give him a call?'" She did, and Byers agreed to meet Royston for lunch in San Francisco the next month, April, when Royston would be traveling there for a medical meeting. Looking back, Royston says, "I'm sure he was just doing her a favor," but the coincidental link turned out to be a marvelous stroke of good fortune. Many years later, Ted Greene, who was hired by

Byers in 1979 to serve as Hybritech's president, would remark: "Now this is the way great companies get started. It's who you've dated, you know."[1]

Byers had just recently become a junior partner in Kleiner, Perkins, Caufield & Byers, a San Francisco and Menlo Park venture capital firm. The partnership of Mr. Kleiner and Mr. Perkins began in 1972. Eugene Kleiner was a mechanical engineer from New York, soft-spoken and reserved. In 1955, he was hired at Shockley Semiconductor, one of the first electronics firms in the new industry growing up at the time around Stanford University. He soon became disenchanted with the dictatorial management style of William Shockley, the owner. In 1959, Kleiner and seven colleagues left to found a company of their own (a deed for which they acquired the name 'the traitorous eight').[2] The new start-up was funded largely by industrialist Sherman Fairchild, and was called Fairchild Semiconductor. Three years later, Fairchild purchased the ownership shares of the original founders. The eight engineers then quit the company and went on to build another generation of high-tech firms in the area. Their exodus from Fairchild to nearby entrepreneurial pastures was a seminal event in the creation of Silicon Valley. Kleiner's new electronics firm, called Edex (it produced educational devices), was successful, and soon purchased by Raytheon. Having by then established numerous contacts with Silicon Valley inventors and investors, Kleiner decided to go into venture capital.[3]

---

[1] UCSD CONNECT video, "Meet the Entrepreneur," May 1991.

[2] "Eugene Kleiner, Early Promoter of Silicon Valley, Dies at 80," New York Times, November 26, 2003.

[3] Among Kleiner's earliest and most important connections was influential East Coast investor Arthur Rock. Kleiner's transition from engineer and entrepreneur to venture capitalist began when he was offered an opportunity to participate as a limited partner in a fund raised by Rock and an associate,

Several years later, while looking around for a partner, Kleiner was introduced to Thomas Perkins. Perkins was an electrical engineer and Harvard Business School graduate from White Plains, New York. At Harvard in the late 1950s, he studied under Georges Doriot. Doriot had been instrumental, a decade earlier, in establishing ARD, the American Research and Development Corp., in Boston. ARD was the nation's first formal risk capital investment organization. Perkins was offered a job at ARD, but after making the acquaintance of California entrepreneur David Packard at a trade show in New York, he opted to move instead to the West Coast to join Hewlett-Packard. He stayed for five years, and then resigned in order to establish a consulting practice and to get involved as an executive with an entrepreneurial venture called Optics Technology. Optics Technology ultimately failed after Perkins, having run afoul of the owner and the board of directors, was dismissed. Perkins returned to Hewlett Packard (while in his spare time directing a successful company of his own, University Laboratories, a maker of laser devices). During his second stint at HP, he helped orchestrate the company's move into the minicomputer business. Following a series of disputes with Packard over corporate strategy, however, it was time again, in 1972, for Perkins to move on. At that juncture, a friend convinced Perkins that venture investing was what he ought to be doing, and then introduced him to Eugene Kleiner. Although the two had very different personalities – Kleiner was quiet and

---

Tommy Davis. His career in independent venture investing took off in 1968 when Robert Noyce and Gordon Moore, two of his compatriots among the 'traitorous eight' at Shockley and Fairchild, persuaded him to invest in their new engineering venture, a company called Intel. See Chapter Four, pp. 48-64, for brief histories of Silicon Valley and the West Coast venture capital industry.

easy-going; Perkins has been described as "driving," "restless," and "charismatic" – they hit it off.[4]

Kleiner and Perkins rented space for their partnership in a newly constructed tower at One Embarcadero Center, in the heart of San Francisco's financial district. They soon opened an additional office at 3000 Sand Hill Road in Menlo Park. Before long, Kleiner and Perkins found themselves surrounded there by many other firms and colleagues in the blossoming venture finance industry. The Sand Hill Road address quickly became a powerful center of gravity for West Coast risk capital.[5] By 1977, when Byers was brought in, Kleiner Perkins had already established a reputation as an industry leader. Its record of investment successes has since become legendary.[6] The firm raised $7 million for its first fund beginning in 1972, and put that money into seventeen new high-tech ventures. In 1984, it distributed to investors securities in those firms worth $218 million. By the end of that same year, the partners had raised and invested an additional $200 million, and the entrepreneurial computing, software, internet, and biotech companies in Kleiner Perkins' portfolio had achieved an aggregate market value of nearly $5 billion. The returns and the magnitudes of the investments were astonishing. Kleiner Perkins' success was a big part of the rapid expansion of the West Coast venture capital industry during the late 1970s and early

---

[4] The Kleiner Perkins story is told in John W. Wilson, The New Venturers: Inside the High-Stakes World of Venture Capital, Reading, MA: Addison-Wesley, 1985; ch. 5.

[5] "Now, firms are more than happy to pay upward of $70 per square foot for office space on Sand Hill, even when excellent space can be had nearby for half that cost. And firms that already hold space are willing to cram and contort growing operations into tiny spaces to preserve the special status of the Sand Hill letterhead." Clifford Carlsen, "Sand Hill Road Still the Address of Choice for VCs," San Francisco Business Times, May 10, 1999.

[6] Wilson, The New Venturers, ch. 5.

1980s. Among the "market-defining ventures" (as the firm describes its portfolio companies)[7] to which Kleiner Perkins has provided funding and early-stage strategic and managerial assistance, are marquee (and, in some cases, household) high tech names, such as Amazon.com, America Online, Compaq Computer, Cypress Semiconductor, Electronic Arts, Lotus, Netscape, Sun Microsystems, Tandem Computer, WebMD, and Wyse Technologies. By 1978, Kleiner, Perkins, and their new partners, Frank Caufield and Brook Byers, were already leading the way in biotechnology, too, with stakes in Cetus, Genentech, and Collagen, Inc. These were the people with whom, by chance, Royston and Birndorf now found themselves mixed up.

In 1978, Brook Byers was thirty-two years old. He held a degree in electrical engineering from Georgia Tech. After graduation, he had worked for a time as an engineer with the Federal Communications Commission. He then decided to enroll in the Stanford University MBA program. Upon picking up his credential there in 1972, he began serving an apprenticeship to Silicon Valley venture capitalist Franklin 'Pitch' Johnson. Johnson was a graduate of Palo Alto High School and, like Tom Perkins, a student of Georges Doriot at the Harvard Business School. He is recognized today as a West Coast risk capital pioneer.[8] In 1962, he and partner Bill Draper secured an SBIC (small business investment company) license and raised what was, in essence,

---

[7] Go to the company website at www.kpcb.com.

[8] On venture capital pioneers in the Bay Area, see Martin Kenney and Richard Florida, "Venture Capital in Silicon Valley: Fueling New Firm Formation," pp. 98-123 in Understanding Silicon Valley: The Anatomy of an Entrepreneurial Region, ed. Martin Kenney, Stanford, CA: Stanford University Press, 2000.

one of the earliest venture funds in Silicon Valley. Since 1965, Johnson has directed his own outfit, called Asset Management, while occasionally teaching finance classes at the Stanford Business School, and serving numerous civic and professional organizations in a variety of capacities. For a time, he was a director of the National Venture Capital Association. He enjoyed a major success in biotechnology following an early investment in Amgen, where for many years he sat on the board of directors. Johnson mentored Byers, and ushered him into the inner sanctum of the Bay Area investment community.

The local venture capital industry was still relatively small. "At the time," Byers says, "there were only about a dozen young associates working with venture funds in the area. We all knew each other."[9] One of the peers with whom Byers came into contact was Bob Swanson, who would soon become a founder of Genentech. The two were very close in age. Swanson was a junior partner at Kleiner Perkins. Byers and Swanson struck up a friendship and even shared an apartment for a time in the swanky Pacific Heights section of San Francisco, a place with a view of the Golden Gate Bridge. Swanson introduced Byers to biotechnology. While contemplating the Genentech idea, he discussed it with Byers. When Swanson wrote up the Genentech business plan, he asked Byers to proofread it. Later, when it came time to move Genentech from Herbert Boyer's UCSF laboratory, Swanson turned to Byers again. His friend and associate located vacant warehouse space for the company in South San Francisco, through a personal connection in the local real estate business. Kleiner and

[9] Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, Cambridge, MA: Perseus Press, 2000; p. 15.

Perkins learned of Byers through his associations with Johnson and Swanson. They were aware of the assistance that he lent to Genentech, but the young man especially impressed them with his savvy and commitment in 1975 when he became involved in the syndicated financing of the Tandem Computer start-up. Kleiner and Perkins were particularly high on the prospects of the company, but they had trouble convincing other venture financiers to buy into it. Byers stepped in to help make the deal go. He not only pledged money raised by Johnson for Asset Management to the company; he invested some of his own cash, as well. In 1977, Byers received an invitation to join Kleiner Perkins as a full partner. He accepted.[10]

In March of the following year, Byers received the phone call from Royston's wife, and agreed to meet with the young physician. The personal connection was crucial. Venture capitalists typically do not accept unsolicited proposals. Common wisdom in the field says that they are costly to evaluate and unlikely to justify the expense and effort.[11] Just as important as the personal referral were Royston's credentials. His Stanford and UCSD affiliations signaled that he was the genuine scientific article, and probably knew what he was doing when it came to the technology. Drawing on his experience with the Genentech and Collagen, Inc. examples, Byers was willing to listen to Stanford and UC inventors or proprietors. So, Royston had his foot in the door, and now had to make the most of it. Birndorf was

---

[10] Robbins-Roth, From Alchemy to IPO, p. 17.

[11] On the importance of social connections in attempts to attract venture funding to high-tech start-ups, journalist Gary Rivlin remarks, "Venture capitalists like to claim that a person arriving on Sand Hill Road needs nothing more than a good idea and the requisite moxie to receive financing. In reality, though, most entrepreneurs cannot even secure an appointment inside most of the top-tier firms unless they have attended the right schools, come from the right families or can drop the right names." See

confident that his partner could effectively pitch hybridomas and monoclonals. He saw in him the characteristics of a good salesperson: "Ivor is a very exuberant, high energy person, and this was, you know, twenty years ago, and he was in his early thirties. He was young and excited and infectious." On May 1, 1978, Royston and Byers met for lunch. To the venture capitalist, the doctor explained hybridoma technology and its possible commercial applications, in much the same way he once reported to the Chessmen, the members of his high school investment club, about opportunities for purchasing discounted second mortgages, and in much the same way he was accustomed to presenting in grant applications the potential medical benefits of biological research. Having learned of Kleiner Perkins' involvement in Genentech, Royston elected to highlight 'cloning' in his explanation:

> I sat down with Brook and I said the magic words. I remember very distinctly. Because I knew his firm was involved with Genentech, I just said, 'Look, you guys know how to clone genes. We're talking about the same thing, only we're cloning antibodies. And I sketched on a napkin how to do that. And the point I made with him was, just like you can clone genes, you can clone antibodies, because hybridomas lend themselves to cloning. If you clone antibodies, you can make unlimited amounts of these specific antibodies that can be useful for diagnostics and therapeutics. He immediately became very intrigued with the whole thing. You see, it was just the question of using the right words, because their Genentech experience had primed them for another opportunity in immunology.

THE BUSINESS PLAN

Culturing hybridomas (i.e., cloning antibodies) and synthesizing nucleic acid sequences (cloning genes) are two very different procedures, but Royston apparently made his point. Byers requested a business plan. According to Royston, he said,

---

Gary Rivlin, "An Investor's 'Gong Show' for Billion Dollar Dreamers," New York Times, July 5, 2004.

"'Well, Ivor, go back home, write down some of these ideas on a piece of paper – it doesn't have to be very long – and send it to me." So, Royston returned to San Diego. He and Birndorf organized their thinking and research on the project, and one week later, on the 8th of May, put a business plan in the mail (along with some scientific papers on hybridoma technology, and résumés from both Royston and Birndorf). The proposal was six pages long. It began with a brief primer on the basics of immunology, the medical uses of antibodies in blood typing and screening and various kinds of diagnostic testing and monitoring, conventional methods of manufacturing polyclonal antibody sera, and a short discussion of the fundamental principles and advantages of hybridoma technology. Royston and Birndorf summed up their plan in this way:

> We now propose to make antibodies according to a newly discovered technology which does away with large animals and allows pure antibodies to be made by cells growing in tissue culture flasks. The cost will be only a fraction of the cost utilizing the standard methods, the amount of antibody produced will be unlimited, and the product will be pure and therefore monospecific.

The next section presented information about Royston and Birndorf, the designated 'founders,' and the academic research in immunology and oncology that was being conducted with monoclonal antibodies in Royston's laboratory at the La Jolla VA Hospital and elsewhere (presumably to highlight the long-term potential and breadth of applicability of hybridoma technology). Birndorf then contributed sections that analyzed the existing commercial market for antibodies and the competition that the proposed venture would likely face. Royston discussed the proprietary status of hybridoma technology with respect to patents and intellectual property law. The final

two pages of the plan outlined the material and organizational requirements of the start-up, specific tasks that would be assigned to each of the founders and additional personnel, and an operating budget for the first year. The tentative name for the proposed company in the business plan was 'Hybrotec,' short for hybridization technology.

Birndorf's market analysis summed up the business opportunity. The consumers of commercial antibodies include most hospitals, blood banks, clinical medical laboratories, and academic bioscience labs. Producers sell hundreds of different kinds of antibodies. In 1978, the price for polyclonal antibody mixtures ranged between five and twenty dollars per milligram, depending on the type and the purity of the serum. The top-selling antibodies, according to the 'Hybrotec' business plan, were those directed against hepatitis and other viruses (including influenza and herpes), human red blood cells (type A, B, and AB), numerous human immunoglobulins in the blood, human blood proteins (complement, fibrin, transferrin, haptoglobin), and bacteria of various kinds (salmonella, E. coli, neisseria, and shigella).[12] Royston and Birndorf believed that, by employing hybridoma technology, they would be able to reduce considerably the costs of antibody-making, while delivering a superior product – antibodies with greater specificities that could perhaps be selected for high affinities to their targets, as well. They planned to sell their superior antibodies for half the price of ordinary polyclonal mixtures. The prospectus' statement of the firm's business objective revealed both the audacity and naivete of the new entrepreneurs: "the aim will be to capture the entire market."

Byers had asked Royston to identify firms against which the proposed start-up would be competing in the marketplace. Birndorf did the research and cited Burroughs-Wellcome, Litton Bionetics, Cordis Laboratories, Hyland Diagnostics, Difco Laboratories, and Behring Diagnostics – all large manufacturers of antisera for medical and research purposes – as possible competitors. These companies employed conventional methods to produce polyclonal mixtures. They stabled, immunized, and bled animals (mostly horses, goats, and sheep), and then separated and 'purified' the immunoglobulin-containing sera from the blood. When Royston looked for firms moving to exploit hybridoma technology, he found "nothing out there."[13] In the business plan, he and Birndorf maintained that cell hybridization procedures therefore offered a huge technical advantage, and an opportunity for a new entrant in the field to challenge established leaders. The authors recognized, though, that the window for exploiting this technological edge would probably not remain open for long. Hybridoma technology belonged, for the moment, to a small clan of academic immunologists, but if it appeared to be commercially viable, then others would surely attempt to acquire and adopt it. Royston and Birndorf estimated that it would take competitors about a year to catch on and switch over their antibody production systems to the new method:

> Only a dozen university laboratories in this country are currently doing research using antibodies produced by hybridomas, so the number of

---

[12] Strains of HIV have since become leading antigens, too, of course.

[13] Actually, Royston did come across one small firm in England, called Seralabs, that was preparing to make monoclonal antibodies. The company had just received a development grant of £100,000 from the British government for that purpose, and soon changed its name to Celltech. Celltech is still in business. It has been manufacturing monoclonals for over twenty-five years, and has undertaken research on monoclonal-based therapeutics, but it never came close to achieving the kind of commercial success in diagnostics that Hybritech would enjoy within just a few years.

> people with the necessary experience to enter into commercial production is very limited. This is not to say that the situation will stay the same much longer. I predict that within the year, companies will have to begin production of hybridoma-produced antibodies.

Regarding the important matter of intellectual property rights, Royston noted that the procedures for establishing antibody-producing hybrid cells had already been published. The technical basis for the company was not an invention of the entrepreneurs, and not a process that they could protect and monopolize with patents. The technology, Royston reported, "probably belongs to the Cambridge scientists [Köhler and Milstein] who discovered the idea." However, he also intimated that "we are currently modifying the published procedures such that there may be a good possibility that our process will be patentable." Further, making reference to preliminary rulings on the patentability of biological organisms issued by the U.S. Court of Customs and Patent Appeals and the U.S. Supreme Court in the case of Diamond vs. Chakrabarty, Royston predicted that specific hybridomas and monoclonal antibodies developed for specific biochemical applications would likely qualify as patentable inventions.[14] He stated his intention to seek patent protection for every hybridoma line that he and Birndorf could establish in cell culture.

---

[14] See United States Supreme Court, Diamond v. Chakrabarty, 447 U.S. 303, 1980. The specific question to be answered in the case was whether patent protection would be extended to bacteria genetically engineered to break down crude oil. The general legal principle at stake was whether living things could be patented. The court ruled that while 'natural' phenomena directly put to human ends without modification cannot be claimed as inventions, artificial, genetically engineered bacteria might be, if it was established that they satisfied the usual requirements for patent protection – that is, if they were 'compositions of matter' that were both novel and useful, and if their design and manufacture were not generally recognized by practitioners in the field to be obvious extensions of prior art. The court ruled, in effect, that life is a philosophical and taxonomic matter. According to the published opinion of the court in the case, authored by Chief Justice Burger, the fact that the microorganisms were alive was legally irrelevant. In 1978, Royston and Birndorf anticipated, on the basis of preliminary rulings in Diamond v. Chakrabarty, that both myeloma-lymphocyte hybrid cells and antibody molecules would likely qualify as patentable inventions. As it happened, due to the properties of monoclonals, antibody patents were easily circumvented.

The business plan indicated that the company would first attempt to supply antibodies for which demand was the greatest, and that the two principals were ready to start immediately. Royston wrote, "Mr. Birndorf and I are in a good position to begin producing hybridoma antibodies as soon as the venture is funded." The entrepreneurs proposed "to manufacture by the end of the first year ten to fifteen of the most marketable antibodies." They closed the prospectus with an operating budget. Royston and Birndorf stated that they would need money for salaries, laboratory, storage, and office space, along with supplies and equipment (including, microscopes, incubators, refrigerators, freezers, centrifuges, pH meters, balances, and a gamma counter). The plan called for Birndorf to leave the employ of the university to serve as the company's full-time scientific director. He remembers, "I was going to get a $5,000 raise to $20,000. And we had [planned to hire] all these technicians. It was me and six other people total." To grow hybridomas, screen monoclonals, and manufacture batches of antibody at industrial scales, the company intended to hire, in addition to Birndorf, an immunochemist at an annual salary of $20,000, two tissue culture technicians and two general lab technicians, each at $12,500 per year, and an additional assistant for $8,000 per year. Royston would serve as an unpaid consultant. The entrepreneurs elected to commence operations without an administrative staff. They indicated that they would first start making antibodies and then recruit a controller, office help, a sales and marketing team, and personnel to handle others functions "as necessary."

Birndorf estimated that the operation would require a lab of about 1,000 square feet, along with a mouse cage room of 400 square feet. He found vacant lab space

outfitted with benches, cabinets, and tissue culture hoods available for rent in the Microbological Associates Building on Science Park Road, just north of the university on Torrey Pines Mesa, and in a building on Prospect Street in downtown La Jolla, just south of the university, a structure formerly occupied by the Scripps Clinic and Research Foundation. The former property included access to a shared cold room, library, and cafeteria. The operating budget allotted $22,000 for renting laboratory facilities. Anticipated personnel costs for the first year totaled $98,000. $25,000 was budgeted for supplies, and $33,000 for start-up equipment. In all, Birndorf says, "We wanted $178,000 for the first year." Royston and Birndorf suggested offering stock options to employees as incentives and compensation for the low salaries. They did not propose a definite split of ownership shares. If there were standards or conventions applicable to equity arrangements in this kind of high-tech venture, Royston and Birndorf were not aware of them. In the face of uncertainty on the matter, the entrepreneurs stated only that "ownership will be initially vested in the founders and equity investors. The percentage of ownership is to be negotiated."

Byers read the plan and shortly informed Royston that the general partners of Kleiner Perkins wanted to visit San Diego, to see the laboratory and meet the researcher and his assistant. The partners, he said, were intrigued by the scientific, commercial, and legal aspects of the proposal, but before beginning a thorough technical assessment, they wanted to get to know and evaluate the scientists. And, so it was that, in June of 1978, Royston and Birndorf, with the help of another lab assistant, prepared to "put on a show" for the potential investors. All four partners, Kleiner, Perkins, Caufield, and Byers flew down from the Bay Area for the event.

Apparently, they were taking the plan seriously. "It was," says Royston, "the only time I ever saw all four of them together." The venture capitalists stayed at the posh La Valencia hotel in downtown La Jolla, overlooking scenic La Jolla Cove. In the morning, they traveled a couple of miles to the north, on a steep, winding canyon road, to Royston's tiny VA Hospital laboratory. They spent most of the day taking in a hybridoma-making demonstration given by Birndorf and talking about Royston's work at the UCSD School of Medicine. Royston was using monoclonals to characterize the molecular structures and compositions of lymphoma and leukemia cells. The antibodies were employed to identify and map specific antigens on cell surfaces.[15] The researchers had hybridomas positioned beneath a microscope so the venture capitalists could look at them. They also had a gamma counter monitoring a radioimmunoassay, printing out numbers that represented levels of antibody-cancer cell binding activity. Late in the afternoon, Royston and Birndorf drove the venture capitalists to the airport. The group of six went into the terminal and sat in a small airport lounge to conduct business. Tom Perkins was the principal spokesman for the venture investors, and he dominated the conversation. Royston remembers Perkins asking him:

---

[15] I. Royston and R. Levy, "Neoantigens on human lymphoblasts detected by monoclonal antibodies produced in vitro," pp. 251-353 in Advances in Comparative Leukemia Research, 1979, eds. D.S. Yohn, B.A. Lapin, and J.R. Blakeslee, North Holland, NY: Elsevier, 1980; I. Royston, J.A. Majda, S.M. Baird, B.L. Meserve, and J.C. Griffiths, "Human T-cell antigens defined by monoclonal antibodies; The 65,000 dalton antigen of T cells (T65) is also found on chronic lymphocytic leukemia cells bearing surface immunoglobulin," Journal of Immunology, 125: 725-731, 1980; I. Royston, J.A. Majda, G.Y. Yamamoto, and S.M. Baird, "Monoclonal antibody specific for normal and neoplastic T cells," pp. 537-540 in Protides of the Biological Fluids, Proceedings of the 28th Colloquium, ed. H. Peeters, Oxford: Pergamon Press, 1980; R. Taetle and I. Royston, "Human T cell antigens defined by monoclonal antibodies. Absence of T65 on committed myeloid and erythroid progenitors," Blood, 56:943-946, 1980.

> 'What is it going to take, Ivor, to make monoclonal antibodies outside of your laboratory?' Howard and I had already worked out a budget, and we said, 'Well, we need a couple of hundred thousand dollars to do this.' And Perkins said, 'I'll give you three.' Those were his words at the airport. 'We'll give you three hundred thousand dollars' – for proof of principle [evidence that the technology works as advertised], we'll give you three hundred thousand dollars. Now show us you can make some antibodies outside the lab. 'What's the most common antibody used today in medicine?' It was hepatitis antibody because every unit of blood is screened for hepatitis antibody using an antibody test kit, so I said, 'Hepatitis. We'll make hepatitis antibodies.' And so he said, 'We'll give you three hundred thousand dollars.

Birndorf also remembers the conversation well, because it was, he says, "the first and last time anybody ever offered us more than we were asking for." Apparently, the Kleiner Perkins delegation had arrived in San Diego prepared to offer $300,000 unless something they observed or learned in their talks with the scientists gave them pause. They also came carrying, it seems, a definite notion about how the ownership shares of the proposed firm would be structured. According to Royston, Perkins suggested that: "'We'll own sixty percent of the company and you guys – you, Howard, and all future employees will own forty percent.'"[16] There wasn't any haggling. The young and inexperienced academics were out of their depth. They accepted the terms. The six-page business plan that led to Kleiner Perkins' investment pledge eventually became the subject matter of a case study at the Stanford Business School, in Franklin 'Pitch' Johnson's course on entrepreneurship – Business 354. For a number of years, Johnson invited Royston to Stanford to speak about the plan, and when he did, the guest invariably impressed his audience: "It's the only place,"

[16] In fact, when the deal was closed, Kleiner Perkins took 300,000 shares of preferred stock, while Royston and Birndorf divided 115,000 (unequally – 85,000 for Royston, 30,000 for Birndorf). So, the final split was more than 70% for the venture capitalists and less than 30% for the entrepreneurs.

Royston says, "I've ever lectured and gotten a standing ovation. I never get standing ovations in medical school, but in business school, I get them." The sole point on which Johnson's students found fault, however, was the ownership split. They generally agreed that the entrepreneurs gave too much away. Royston says, "That's the part I was criticized on by the Stanford business students." Still, he defends the deal. "We had no money. We were unknown scientists with no track record, just a couple of guys with an idea. It wasn't so bad. Today, would I do it for that? No, I would demand [more].... I'm not an unknown with no track record." Years later, after Hybritech's IPO and subsequent sale had made many millions for everyone involved at the beginning, Royston was able say: "Everybody did well, including Kleiner Perkins. Kleiner Perkins did very well, and I was very fortunate, and so was Howard."

Birndorf was indeed fortunate – no one in his position could have reasonably expected such good luck – and he was excited that he might have a chance to get away from the university and start something for himself. But he also remembers being dissatisfied at the time with his portion of the company. He considered it inadequate given that, in addition to founding the enterprise, he would be operating it for very modest compensation: "I ended up with five or six percent.... I was pretty upset about it since I was the one that was leaving [a job at the university]." Royston's piece of the company would be nearly three times greater. Royston says, "I had a bigger stake than Howard because of my seniority." The two entrepreneurs had considered the issue before, but, according to Birndorf, this particular division of shares wasn't among the possibilities they had discussed:

> It was funny how things changed as we got closer to it being a reality. At first, Ivor said, 'I'll just take ten percent, you take ninety percent, because you're going to go do it.' And then, as we got closer, it was, 'Well, let's do it fifty-fifty.' And then, when we got to the airport, he sure didn't argue or say that we had a fifty-fifty deal. He let it go. I was pretty angry with him at the time. I was pretty perturbed about it.

Birndorf didn't complain about the split or make a counter-proposal before handshakes cemented the tentative deal (although he does remember later calling New York on the telephone to try to persuade Byers to enlarge his share).[17] He didn't receive an invitation, and didn't spy an opening. At the airport in San Diego, the venture capitalists were, for all practical purposes, negotiating with the physician and university faculty member, and not with him. Birndorf, the junior assistant, was just along for the ride. Although the two were friends, Royston remembers that Birndorf was clearly cast in a subordinate role: "I always saw him as sort of a research assistant. Things are different now because Howard has been so successful in his entrepreneurial endeavors in this business, but...I was more of his superior at the time." Birndorf's status afforded no purchase for bargaining:

> Ivor was the M.D. He had the credibility. I was just this lab tech. In retrospect, it was pretty unfair, but I didn't really have a lot to say in the matter. I was sort of locked in, you know. I didn't have a choice – it was either do it or don't do it, and I didn't know what leverage I had at the time. I didn't really feel like I had much, although probably I had more than I thought I did.

---

[17] The call was worthwhile. Birndorf received an additional percentage point share of ownership. After a forward split – in which the number of outstanding shares was simply multiplied by five – Birndorf held 150,000 shares of preferred stock. He had paid .02 cents for each. When the price of Hybritech shares reached an apex of thirty dollars each in 1983, Birndorf's piece of the company was worth $4,500,000.

DUE DILIGENCE

Following the partner's visit to San Diego, Byers immediately began investigating the details of the investment opportunity: "I spent the next three months doing due diligence."[18] He needed first to assess Royston and Birndorf's claim that there would, indeed, soon appear an emerging market for monoclonal antibodies. For this, he had to canvas opinions from scientific experts. Apparently, the consultants on whom he relied – reportedly research directors of major pharmaceutical companies – confirmed what Royston had told him about hybridomas and monoclonals, because Byers continued looking into the idea.[19] Royston remembers worrying that the consulting experts wouldn't grasp the concept because monoclonal antibodies were so new. The potential of hybridoma technology was evidently not obvious to everyone.[20] But his fears were not confirmed. Byers was exposed to liberal opinions, and Royston acknowledges his debt to the individuals who expressed them: "I was lucky."

---

[18] Robbins-Roth, From Alchemy to IPO, p. 51.

[19] According to John W. Wilson, the pharmaceutical executives questioned by Byers acknowledged the theoretical potential of monoclonal antibodies, but also indicated that they had no immediate plans to develop faculties and capabilities in cell biology or immunology. See Wilson, The New Venturers, pp. 82.

[20] First-hand stories of skepticism among pharmaceutical and diagnostics executives regarding the commercial utility of monoclonal antibodies are told by two industry persons who later became Hybritech officers. Early in 1979, Ted Greene tried to convince scientists and businesspersons at Syntex that hybridoma technology was an important development, but he reports being told that "'monoclonal antibodies were academic curiosities that would never amount to much.'" See chapter seven, below, pp. 34-39. David Hale, who succeeded Greene as Hybritech's president, was working in the diagnostics industry in 1980, for Becton Dickinson, a company that Brook Byers had identified as a likely competition for Hybritech in the course of his due diligence research. Around 1980, Becton Dickinson began investigating monoclonal antibodies. According to Hale, the firm "came to the conclusion that they were never going to work." See also, "Monoclonals Wage Uphill Struggle for Lion's Share of Diagnostic Test Market," McGraw-Hill's Biotechnology NewsWatch February 4, 1985: 6.

Byers proceeded with his inquiries, and his education in the commercial uses of antibodies led to an important shift in strategic direction while the company was still little more than a few pages of sketchy blueprints and projections. Looking back at the market analysis section of the business plan, Birndorf notes: "It's an antibody market, so, we were thinking, still, about selling antibodies...this is still pure antibodies." Byers saw that there was a better way to make money on monoclonals than simply growing them and selling them by the gram. He targeted a new market for the proposed start-up to enter – the in vitro diagnostics industry. Royston had explained to Byers that antibodies were utilized by hospitals, clinical laboratories, and blood banks as reagents in diagnostic tests – immunoassays in which the binding properties of antibodies permit the detection and fine measurement of an expanding universe of analytes (substances to be identified and quantified, e.g., pathogens or markers of disease) in biological samples. He had suggested selling antibodies to academic and medical researchers, and to clinical laboratories. But, in the course of his research, Byers learned that antibodies usually enter clinical laboratories as components of pre-packaged test kits that include reagents, instrumentation, and supplies. Laboratories generally purchase these experimental systems rather than designing and assembling their own because the use of standardized kits increases efficiency, throughput volume, consistency, and control, while reducing labor costs. Byers also learned that monoclonal antibodies could substitute for polyclonal mixtures in most diagnostic immunoassays, and that the substitution could improve the performance of these tests in terms of speed, accuracy, and reliability.

Royston had introduced Byers to monoclonal antibodies by emphasizing their homogeneity and specificity. He had talked about cloning antibodies as something akin to what Genentech was doing with genes. However, after becoming familiar with the diagnostics business, Byers, the electrical engineer, recalls that he started working with a different analogy: "What struck me was the analogy to Intel, which replaced ferrite core computer memories with silicon. When you change a fundamental raw material, whatever that material is used in is going to be enhanced."[21] Monoclonal antibodies promised to raise technical standards in the diagnostics business, and in immunoassays, particularly. And it was possible that these improvements could be accomplished without significantly increased production costs, so monoclonal-based tests could conceivably be marketed at competitive prices. Royston notes: "The actual cost of the antibodies was just pennies, in terms of making the kit itself [which also consisted of] plastic and the glass and the bottles....only minute amounts of antibody were needed, you know, microgram amounts of antibodies, so you could make very large amounts of test kits with a small amount of antibody." Finally, a bit of research showed Byers that the potential market for these products was massive.

Royston and Birndorf had a good idea for commercializing hybridoma technology. The business model that they envisioned – selling antibodies in bottles – appeared to be viable, and perhaps they would have had a good chance for success at it, but the idea didn't display the profit-generating potential that venture capitalists typically find attractive in investment opportunities. Venture capital is a risky business. Players in the field require huge returns from their successful portfolio

[21] Wilson, The New Venturers, pp. 81-82.

companies in order to cover the massive losses they incur with failures. They know they will see numerous misses and just a few hits among their unproven technology investments, so they are highly selective. Byers saw that the market for monoclonal antibodies as research products would probably remain limited, but that diagnostics was a field with room for growth. Royston credits Kleiner Perkins with recognizing "that the real power of the antibodies was to use them as ingredients in special diagnostic kits." Birndorf also acknowledges that while he and Royston were hoping to catch on somewhere in the minor leagues, the venture capitalists wanted to hit home runs in the majors:

> We weren't thinking as big as Tom Perkins and Brook Byers were. I mean, they were thinking in terms of, worldwide, a $100 million market. We were thinking, well, we would have been happy with a nice business that generated an income of $100,000 a year to each of us. That would have been fine.[22]

Byers and his venture partners mostly ignored Birndorf's market analysis. They imagined that they might eventually match the monoclonal start-up against stiffer, more powerful competition – a daunting roll of immunoassay and automated analyzer manufacturers including names such as Johnson & Johnson, Abbott, Syva, Baxter Travenol, Beckman, American Hospital Supply, Roche, Becton Dickinson, Coulter, Technicon, and DuPont. The path to profits via this route would be longer, riskier, and far more complicated and difficult, especially since no one involved in the project at the time had any experience at all in the diagnostic testing business, but if things were to go well, it could be far more rewarding. If a new company was able to stake a substantial claim within the in vitro diagnostics industry by incorporating

monoclonal antibodies into clinical laboratory testing – and the general partners at Kleiner Perkins became convinced that this was going to happen – then investors would walk away with a very big score. The diagnostics industry is highly competitive, but also solidly profitable for firms that can capture substantial market shares. The enormous potential upside in this particular investment opportunity made it an attractive one.[23]

Having established that there were potential markets of sufficient size for monoclonal antibodies, Byers also needed to determine whether the two young entrepreneurs could, in fact, secure a competitive advantage within them. An important issue to clarify was the proprietary status of hybridoma technology. Both the initial and long-term prospects for the company were premised largely on the free use of Köhler and Milstein's techniques. Byers knew that Tom Perkins would have to be persuaded that the coast was clear for Royston and Birndorf – legally and competitively – if his firm was going to pony up the requested funds. Perkins had developed a reputation in the venture capital business for evaluating technologies and potential investment deals largely on the strength of entrepreneurs' proprietary positions.[24] In 1984, he told the New York Times:

> What do you look for in a new venture? The answer is simple; knowing when you've got it is the problem. It is a combination of technology and insight into a new market that hopefully the

---

[22] Grant Fjermedal, Magic Bullets, New York: Macmillan, 1984; pp. 95-96.

[23] To add to the attraction, Royston and Byers' consultants had also reported that monoclonal antibodies might eventually be useful as in vivo diagnostics, too, when labeled with radioisotopes or non-isotopic chemoluminescent markers, and in the treatment of diseases, as immune response triggers or delivery vehicles for chemotherapeutic agents.

[24] See Paul A. Gompers and Josh Lerner, The Money of Invention: How Venture Capital Creates New Wealth, Boston, MA: Harvard Business School Press, 2001; p. 47.

> entrepreneur has identified as an emerging market. You have to have enough technology to have a competitive advantage in the market so the product can't be copied right away. The theory is simple. The reality is complicated....It's a matter of experience and judgment.[25]

In this instance, the reality was more surprising than it was complicated. What Byers learned was encouraging. "When I flew to England," he says, "to meet with the MRC folks [the British Medical Research Council – the sponsors of Milstein's Cambridge lab], I found that Milstein had not filed patents for making hybridomas."[26] Royston puts it bluntly: "That was one major mistake." Apparently, it was the sophistication and esoteric nature of the work in Milstein's laboratory that prevented the MRC from recognizing the import of the invention. Köhler and Milstein concluded the 1975 announcement of hybridoma technology by stating that it "could be valuable for medical and industrial use."[27] They immediately approached the MRC to recommend a patent filing. After a cursory review, the agency judged that the invention did not merit the expense.[28] The MRC simply didn't realize what it had on its hands. Americans, including Royston, Birndorf, and Kleiner, Perkins, Caufield and

---

[25] Susan Chira, "Talking Business with Perkins of Kleiner Perkins: Venture Capital Then and Now," New York Times, August 28, 1984: D2.

[26] Robbins-Roth, From Alchemy to IPO, p. 51.

[27] G. Köhler and C. Milstein, "Continuous cultures of fused cells secreting antibodies of predefined specificity," Nature, 1975, 256: 495-497.

[28] See César Milstein, "With the Benefit of Hindsight," Immunology Today, 2000, 21, 8: 359-364; and "Patents on Scientific Discoveries Are Unfair and Potentially Dangerous," The Scientist, November 1, 1993: 11; E.M. Tansey and P.P. Catterall, "Monoclonal Antibodies: A Witness Seminar in Contemporary Medical History," Medical History, 1994, 38 (3): 322-327; and E.M. Tansey and P.P. Catterall, eds., "Technology Transfer in Britain: The Case of Monoclonal Antibodies; Wellcome Witnesses to Twentieth Century Medicine," Contemporary Record, 1995, 9: 409-444; Nicholas Wade, "Inventor of Hybridoma Technology Failed to File for Patent," Science, 1980, 208: 693.

Byers rushed in to seize the opportunity created by the MRC's inaction.[29] The British have been sore about it ever since. A sympathetic American commentator has said: "Anonymous administrators responsible for such decisions should be publicly exposed for their bad judgement and incompetence. Perhaps the time has come to restore the stockades and gallows at Tyburn as a way of reintroducing accountability."[30]

In retrospect, considering the amounts of capital that monoclonal antibodies have since attracted and generated, the MRC's decision to release hybridoma technology was a gaffe of titanic proportions. It was a major blow to British biotechnology, but yet another terrific stroke of luck for Royston and Birndorf, and for Kleiner Perkins, Hybritech, and San Diego, as well. After discovering that the MRC had failed to secure the commercial franchise, it seemed to Byers that Royston and Birndorf's proposed company had only green lights and blue skies ahead. The start-up was free to apply hybridoma technology without a license. It also appeared to have an insurmountable lead in the race to exploit the technique, at least for the immediate period of its founding, early growth, and initial entry into the marketplace (for the starting gun had yet to be fired for all competitors to hear, and, in fact, few of the eventual entrants had, at the time, even considered registering for the contest). Given this circumstance, Byers had little trouble convincing his partners that, from both a technological perspective and an intellectual property perspective, the plan of the enterprise was sound.

---

[29] Other early jumpers included Hilary Koprowski and collaborators at the Wistar Institute in Philadelphia.

[30] Fred S. Rosen, "The Specific Notion," Nature, 1996, 383: 777.

MONEY AND CONTROL

While Byers was checking out the opportunity for Kleiner Perkins and the institutional investors they represented, he also began laying the organizational foundations of the company. The venture capitalists had experience in this area – they knew how to start and run companies. They had done it before, many times. The two academic entrepreneurs had not. At the end of the summer, Byers contacted the pair to tell them that Kleiner Perkins had decided to move forward with the deal. The venturers then selected attorneys to handle patent and corporate matters for the new company. For guidance on intellectual property issues, they turned to Lyon & Lyon, a specialized firm based in Los Angeles. The first lawyer handed the Hybritech assignment was Tom Kiley, who later moved north to work for Genentech. He soon met with Royston and Birndorf to learn about hybridoma technology and monoclonal antibodies. Then, to set up the new company as a legal entity, and to oversee matters related to formal corporate structuring, Kleiner Perkins picked a large and well-known Bay Area business law firm, Pillsbury, Madison, & Sutro. Hybritech was officially incorporated on September 14, 1978. A meeting to close the financing was scheduled for October 18, in the Pillsbury, Madison & Sutro offices in San Francisco, after which the process of building an actual company – with personnel, equipment, and a place to call home – would commence in earnest.

The partners at Kleiner Perkins had constructed a good deal for themselves if the venture should become profitable, but they didn't intend simply to wait for the two entrepreneurs to do it on their own, unsupervised and unmonitored. After striking their tentative bargain with Royston and Birndorf in June, the venture capitalists began

making significant strategic, organizational, and managerial contributions to the enterprise. From the outset, from the beginning of the due diligence phase of the process, the new investors acted, not just as financial partners and sources of capital, but as directors and executives. The consequences of many decisions they made in 1978 were far-reaching, and Kleiner Perkins' influence on the company continued throughout Hybritech's career as an autonomous organization. Well aware of endemic conflicts of interests in relationships between venture capitalists and entrepreneurs, Perkins and Byers both took seats on the firm's board of directors (which Perkins dominated, by all accounts, even though Byers was named the official chairman). From these positions, they not only provided advice and assistance to the company, but also simultaneously kept their hands firmly on the reins of the firm's governance and strategic direction.

The conflicts that arise between entrepreneurs and venture investors typically revolve around two general issues – money and control. Of course, venture capitalists and entrepreneurs almost always share an interest in commercial success, but venture capitalists must be concerned, not only with nurturing individual start-up companies in their portfolios, but also with serving the interests of the limited partners in their venture funds – the large financial institutions (banks, insurance companies, mutual funds, labor unions, pension funds, college endowments, corporate profit-sharing plans, etc.) that trade securities in large volumes and set aside portions of their reserves for investment in high-risk and potentially high return opportunities. Venture capitalists can realize gains and return profits to their limited partners only by cashing in ownership shares and giving up control of companies. Formulating and executing

exit strategies is therefore a key aspect of the venture capital business, and financiers may wish to liquidate their holdings at times that entrepreneurs find inconvenient or deem harmful to their enterprises. There is no shortage of horror stories circulating around high-tech industries concerning unscrupulous venturers rushing young start-ups into initial public offerings under unfavorable or less than optimal market conditions, or pressing management teams to accept acquisition bids for companies that may still possess chances for significant independent growth. The interests of entrepreneurs and venture capitalists are not identical. And when conflicts arise, entrepreneurs may resent and resist what they consider outside interference. They may not wish to give up control and surrender their 'babies' into the hands of others. They may not be motivated by profit in the same way investors are.

Exits are not the only sources of conflict in relations among entrepreneurs and investors. Another common problem for venture capitalists is the high-tech entrepreneur with a scientific or engineering background and limited business experience who refuses to recognize his or her own executive or managerial limitations. As new high-tech companies move through successive stages of growth, and develop manufacturing and marketing functions in addition to research and development operations, it is not uncommon for boards of directors to recommend or insist that entrepreneurial scientists or engineers serving as executives relinquish decision-making powers and step aside for managers with industry experience. When business and organizational know-how become as crucial to the development of a new firm as scientific expertise and experience in running laboratories and directing research, individuals with industry backgrounds may be better suited for positions of

authority and leadership. If conflicts about the organizational roles of entrepreneurs arise in such circumstances, operational control is usually the issue.

Sometimes, though, money is more directly the point of contention, as in disputes concerning the valuation of firms or technologies, or the distribution of equity. Entrepreneurs do not want to see it, naturally, but venture capitalists have an incentive to dilute entrepreneurs' ownership shares, and, on occasion, they have opportunities to do so. In financing rounds, they will sometimes take advantage of weaknesses in a company's financial position or its progress toward performance benchmarks, in order to take greater stakes for themselves and their limited partners. Access to capital can be a powerful lever for investors seeking to hold sway over a company's decision-making processes. Naturally, diplomacy is often the preferred way of resolving differences between founders and investors (when it works), but not always. Sometimes, venture capitalists are moved by what entrepreneurs and others interpret as greed. In high-tech circles, venturers are occasionally referred to – often humorously, but sometimes bitterly – as 'company nappers' or 'vulture capitalists.'

Partly because of these structured tensions in financier/entrepreneur relations, it has become the custom in the West Coast style of high-tech investing for venture capitalists to become directors of the companies in which they place funds. Often, they go further into active, 'hands-on' managerial involvement that can restrict the operational autonomy of company officers, to greater or lesser degrees. These practices have become conventional because they enable investors to short circuit struggles for executive power that may threaten to diminish market values or block paths to exits. The partners at Kleiner Perkins observed these customs in their

dealings with Hybritech. Brook Byers became intimately involved in the formation and day-to-day operation of the new company, not only to guide and assist the entrepreneurs in order to help them avoid unnecessary losses and steer the firm efficiently toward profits, but also to retain control and protect Kleiner Perkins' interests and prerogatives.

Consequently, a significant portion of the 'entrepreneurial function,' in the case of Hybritech, was assumed by the venture capitalists. Of course, Royston and Birndorf welcomed the assistance and expertise of their new partners, along with the money they provided. The best partnerships between entrepreneurs and venture capitalists are synergistic unions that blend the technical and scientific know-how of the founders with the business experience and acumen of the financiers. This is what occurred in the Hybritech case. Kleiner Perkins' activism took the form of benevolent paternalism. The venture capitalists intended to press their stamp on the new enterprise, but the inexperienced entrepreneurs were pleased to let them. They permitted the financiers to cast Hybritech in the mold of agile, flexible Silicon Valley high-tech start-up operations. Royston and Birndorf did not feel unduly constrained by Kleiner Perkins' (and, in particular, Brook Byers') deep involvement in the company. In fact, they appreciated the degrees of freedom and latitude they were given: "The thing about Brook that's so fantastic," says Birndorf, "is he lets people do things that they've never done before." In the Hybritech case, the entrepreneurs experienced the discipline imposed by the venture capitalists as empowering and enabling.

Byers began shaping the operation from the day of the closing. First, the two entrepreneurs were informed that neither of them would serve as president of the new company. "They [Kleiner Perkins] said it right when they did the deal," Birndorf recounts. "They made it very clear that neither one of us had the background or expertise to be president, and we agreed. I mean, I think we agreed." Byers announced that he would take on the role himself, temporarily, until a suitable replacement with industry experience could be found. And then, Byers relates, Royston and Birndorf were introduced to the spare, frugal, disciplined approach that the firm would adopt when they arrived in San Francisco for the closing: "We started on such a low budget that they stayed at my house and slept on couches. We were going to create the right culture in the company, one that was lean and mean and focused on one thing. If you start a company with this culture it stays with you. But if you start one wrong, you can never correct it later."[31] The partners at Kleiner Perkins assumed control of the company from the beginning, and became its principal architects, at least insofar as the corporate governance of the enterprise was concerned. The venture capitalists acted, in effect, as entrepreneurs themselves.

Shortly before the closing, Byers began traveling regularly to San Diego for meetings with Royston and Birndorf. Birndorf recalls "We used to meet at Ivor's house, off hours, and Brook came down several times, helping me do budgets, and figure out what we needed." The guidance that Byers provided was essential, because, when it came to operating a commercial enterprise, the two academic scientists were complete novices. "I didn't know anything about this kind of thing," Birndorf says,

[31] Fjermedal, Magic Bullets, p. 100.

"and Brook was helping me. He was sort of being my mentor on this." Byers' direct input into the company's daily business activities continued for several more months. Because this assistance turned out to be so valuable, Royston now considers the equity bargain that he and Birndorf struck with the venture capitalists – one in which the two entrepreneurs held less than 30% of the firm – to be a fair one. In his view, Kleiner Perkins' numerous, difficult to quantify contributions were crucial to the project: "You know, Brook Byers would come down and be the acting president, and really put the management team together. They paid for that, so there were all these hidden values that are not on the balance sheet." In this case, the partnership between the entrepreneurs and the venture capitalists was close and mutually beneficial, and it turned out to be long lasting. Twenty-five years later, long after Royston, Birndorf, and Byers had cut their ties with Hybritech, and long after the firm itself was just a memory, this original team would still be working together to start new companies in San Diego's biotechnology industry.

On Wednesday, October 18th, 1978, Royston and Birndorf were in San Francisco for the closing of the financial deal with Kleiner Perkins. They signed all the papers and received the money that would enable them to move beyond the planning stage, to start making the imagined enterprise a real one. Birndorf tells of feeling a bit flustered by the day's events:

> They handed me a check for three hundred thousand dollars, and I flew back to San Diego. I had this crummy old car. I drove away from the airport, and I ran out of gas on the way home. I had this briefcase. I was clutching it. I had this three hundred thousand dollar check in there. It was more money than I'd ever seen in my life.

The next day, Birndorf visited the Bank of America and talked to an account executive named Martha Demsky about the $300,000: "We had it invested," he says, "you know, like you do." He then leased 4,000 square feet of laboratory space and an office at the La Jolla Cancer Research Foundation on Torrey Pines Mesa, across the street from the Scripps Research Institute, just north of the University of California, San Diego. The 'Hybrotech' business plan had stated that 1,000 square feet would be sufficient, initially, but thanks to Kleiner Perkins' largesse the new firm could afford extra room into which it could grow. Birndorf moved in a desk and a telephone, and arranged to have the telephone line turned on. The following day, Friday, was his last as a university employee in Royston's lab at the VA Hospital. When he left, he carried away some important cargo – cells from Royston's myeloma line. Royston remembers that Hybritech borrowed them free of charge, with no strings attached:

> The cells were transferred from Stanford to UCSD without a material transfer agreement, and they came from England to Stanford without a material transfer agreement, so they went from UCSD to Hybritech without a material transfer agreement. Today, you would have an agreement of some kind, and usually those agreements say you won't commercialize [the material] without approval of the [lending] institution, but those things were not in place.

On Monday, October 23, Birndorf showed up for work at his new job: "I became the first Hybritech employee. I was vice-president of everything, basically, and I was effectively the COO [chief operating officer]." Officially, Brook Byers was the acting president, Birndorf was vice-president, and Royston was an unsalaried consultant. The university had given its blessings to Royston's involvement: "I got all the check-offs and all that. We had lawyers review all that stuff." A bit later, after the lab was equipped and scientific work had commenced, Royston began visiting the

company once or twice a week to look at cells, and keep himself apprised of goings-on at the company. In the very beginning, though, there was nothing much for him to do or contribute. It was mostly up to Birndorf, who had to start from scratch and move the project toward proof of principle – the hepatitis antibodies that Royston and Perkins had discussed in the airport lounge.

Birndorf had a desk and a telephone, and $300,000 in the bank. He didn't have any tools or supplies, and he didn't have any help, but he was ready to proceed and determined to make something happen: "I went in there and immediately started ordering equipment and interviewing people." He made rapid progress. Byers recalls: "I told Howard that if he could make monoclonals to hepatitis B in 6 months, then we'll blast forward. Howard did it in two months!"[32] In that span of time, Birndorf assembled the laboratory and hired a small but talented crew to manufacture the firm's first antibodies.[33] In doing so, he earned Byers' admiration: "The chief laboratory technician for Ivor turned out to be a classic entrepreneur. He turned out to be someone who had that passionate, almost missionary zeal to succeed. And he had a sense of urgency. The anxiety and sense of urgency it takes to succeed, in retrospect, was what I think got Hybritech off to such a lightning-fast start."[34]

Birndorf's first hire at Hybritech, employee #2, was a secretary. The company's third employee was a scientist named Gary David. Slightly built and quiet

---

[32] Robbins-Roth, From Alchemy to IPO, p. 51.

[33] A 1981 publication described the research. See G.S. David, W. Present, J. Martinis, R. Wang, R. Bartholomew, W. Desmond, and E.D. Sevier, "Monoclonal antibodies in the detection of hepatitis infection," Medical Laboratory Sciences, 38: 341-348, 1981.

[34] Fjermedal, Magic Bullets, p. 100.

in demeanor, David was a talented immunochemist. Almost invariably, persons associated with Hybritech in its formative stages attach compliments to mentions of David's intellect, character, and technical achievements. He had previously spent time working in laboratories at the Salk Institute and the Scripps Clinic and Research Foundation in La Jolla, but he had become disillusioned with the politics of academic research and, at the time, late in 1978, he lacked a permanent institutional affiliation. But David was possessed of precisely the background that Hybritech required in order to manufacture its first antibody products and establish a technical lead over the gang of competitors that would soon give chase to the new firm. He became the first of several pivotal hires that keyed Hybritech's early success.

PURE SCIENCE?

Gary David grew up in the 1950s in Big Rock, Illinois, a small country town of five hundred located about sixty miles west of Chicago. He remembers being "always interested in science." The schools serving Big Rock and neighboring towns had few resources for science education, but David read science fiction voraciously from an early age, and displayed a special gift for mathematics. He received a scholarship to attend the University of Illinois, downstate in Champaign-Urbana, in 1960. Without it, he says, he probably would not have been able to leave his small farming community to continue his education. He began his studies as a math major, but then changed direction: "After a couple of years, I realized that I didn't want to spend the rest of my life sitting behind a desk, so I transferred into the microbiology department." There, he took a class on immunochemistry taught by Al Nisonoff. The class was a turning point in David's life and career. It launched him on a journey

through the life sciences that would ultimately land him, fifteen years later, at Hybritech in San Diego, just as the company was getting underway.

Al Nisonoff was a physical chemist who happened to be placed in the microbiology department at Illinois.[35] In 1961, he was already establishing an international reputation for his work in immunochemistry. He eventually became one of the grand old men of the field, which was then being renewed and reshaped by advances in both protein chemistry and biological studies of the immune system. Researchers in the early 1960s were just beginning to employ an array of new tools and techniques to investigate the complex ways in which polypeptides fold and take on or change their shapes – the processes of 'conformation' and 'denaturation' – and the ways in which they interact with each other and other molecules. Some, like Nisonoff, were extending this research to examinations of the structures and functions of immunoglobulins. David received general introductions to protein chemistry and immunology in Nisonoff's classroom, and was stimulated by what he learned: "I started seeing the applications of chemistry in the biological sciences."

He soon became acquainted with Nisonoff's cutting-edge research on the structural aspects of antibody molecules and antigen-antibody interactions. "I took his class during my junior year," David recalls, "and then he invited me to work in his lab

---

[35] Nisonoff explains: "I had published a number of papers and I managed to get a job at the University of Illinois, Urbana, as an associate professor. It was a tenured job. I was an associate professor of microbiology. But, I'd never had a course in microbiology. At that time, microbiology departments liked to have a token immunologist because they make use of immunology in microbiology. So, they didn't care whether I knew any microbiology or not. I would teach a course in immunology. Then two years later, I was a full professor and I still had never had a course in microbiology." See Rutgers University, New Brunswick, History Department: Oral History Archives of WW II; "Interview with Alfred Nisonoff," August 1, 1994.; transcript by Peter Wasek , Jennifer Lenkiewicz, and G. Kurt Piehler; http://fas-history.rutgers.edu/oralhistory/Interviews/nisonoff_alfred.html.

that summer. So, I stayed over and worked as a technician, and got really excited about the technology and the field." The dynamics of protein folding are almost bewilderingly complex. These days, textbooks and modeling software packages depict proteins as swirling, twisting ribbons; or, alternatively, as elongated, densely-packed (but mobile) clusters of small, bound (but active) spheres, each representing a single atom; or, as pastel-colored particle clouds – electrically-charged biochemical nebulae suspended in the microcosm, shape-shifting in atomic force fields. The number of structural permutations to which protein molecules may conform under variable conditions is so large that supercomputers are required to simulate and predict their folding properties and biological activities. So magnificent are these phenomena in their complexity that they attract researchers drawn to the toughest technical challenges. Gary David was one among them. He threw himself fully into the study of antibody proteins.

In the fall of 1964, his senior year, he continued to work in Nisonoff's lab on a part-time basis. Nisonoff gave him a great deal of encouragement and, according to David, was himself still very excited and enthusiastic about the technology and the work. This keeness for the laboratory, along with the consistently high caliber of the research he directed, made the chemist "a wonderful role model." So positive was David's experience that within a year of making his acquaintance with immunochemistry, the young man decided that he wanted to continue working permanently in the field, and to make a career of scientific research. He graduated a semester early with a bachelor of science degree in microbiology and started in immediately as a graduate student at Illinois, working in Nisonoff's group of grads

and post-docs. He began putting in twelve to fourteen hour days, mostly in the laboratory, which he thoroughly enjoyed. "Part of it," says David, "was classes, obviously, but the interesting part was the lab."

As a scientist-in-training, David participated in a number of different projects, all focused on antibody chemistry. Much of the work in Nisonoff's lab involved modeling and manipulating the physical features of immunoglobulins – mapping the molecular structures and kinetics of antibodies, taking them apart, putting them back together, sometimes reassembling them in hybrid configurations, and observing their biological functions and interactions under various conditions. David studied the chemical bonds that, under 'normal' conditions, stabilize antibody molecules in the unique and definite three-dimensional forms that enable them to latch onto specific antigens in specific ways: "We did a lot of chemistry trying to understand the forces involved in interchain associations of the molecule and the correct folding assembly of the binding sites." David's Ph.D. thesis was the characterization of an antibody molecule manufactured by an IgA myeloma cell.[36] One of Nisonoff's former students was a medical doctor who had discovered the disease in one of his patients. Thanks to Nisonoff, David was able to procure samples containing antibody: "It had not been well studied. Certainly, there were very few IgA myelomas around, so I got a bunch of serum from the patient and proceeded to purify and study the myeloma protein. That was my thesis project."

---

[36] G.S. David, "Physicochemical properties of an IgA myeloma protein," Ph.D. Dissertation, Immunochemistry, University of Illinois, 1968.

Due to teaching obligations and problems with access to laboratory facilities during the day – after Nisonoff had left Champaign-Urbana to head the biochemistry department in the School of Medicine at the University of Illinois, Chicago – David's working schedule during his last year of graduate school was awkward and intense. He conducted most of the research for his thesis at night between the hours of 4:00 p.m. and 8:00 a.m. Still, he says, "It was interesting and actually enjoyable." As he was finishing up, he arranged for a two-year post-doctoral research position at City of Hope National Medical Center in Duarte, California, a well known and highly regarded hospital and research institution. Duarte is situated at the upper end of the San Gabriel Valley, just east of Los Angeles, at the foot of the San Gabriel Mountains. Ostensibly, David went to City of Hope to work with a researcher named Charlie Todd, and to gain experience with a more properly biological approach to the study of antibody structures and functions. However, he also had a personal reason for the selection that perhaps outweighed any scientific or professional rationales. David had always wanted to visit sunny Southern California, and the position in Duarte was an excuse to do it: "Ever since I'd learned about water, I'd wanted to come to California, and that was probably a significant part of my choice of City of Hope as a post-doc."

The experiments that David and Todd conducted at City of Hope were exercises in immunogenetics. "I went there," David says, "to work in a rabbit model and try to study aspects of antibody expression by manipulating the rabbit." The idea was to observe under what conditions certain genetic allotypes (variants of specific genes associated with specific phenotypic characteristics – in this case, characteristics of the light and heavy chain components of antibodies) would be expressed or

suppressed. Manipulating the rabbit meant, for instance, transplanting embryos with allotypes for certain antibody characteristics into surrogate mothers that had been immunized against antibodies of that type, or injecting young rabbits with anti-allotype serum, to see how phenotypic expressions of antigenic specificities on the variable regions of the light and heavy chains portions – the binding sites – of antibody molecules (in both homozygous and heterozygous genotypes) would be differentially affected, or not. The results of these experiments were more suggestive rather then definitive – they raised more questions than they answered – but they led to David's first scientific publications, and enhanced his familiarity with antibodies as biological phenomena and research materials.[37] He now calls his fellowship at City of Hope "a good learning experience."

While the technical knowledge and facility that he acquired in Duarte was valuable, David maintains that the greatest benefit he derived from his post-doc experience came through his personal association with Charlie Todd. He had been fortunate to study under Al Nisonoff as an undergraduate and graduate student. Nisonoff had taught him to appreciate learning in the laboratory, to value the process of conducting scientific work for its own sake, for the sheer enjoyment. From that initiation, David carried with him the notion that one did science because it was fun and a means of self-expression. Todd reinforced the lesson. He adopted a relaxed

---

[37] G.S. David and C.W. Todd, "Suppression of heavy and light chain allotypic homozygous rabbits through embryo transfer," Proceedings on the National Academy of Science, USA 62: 860, 1969; M.W. Steward, C.W. Todd, T.J. Kindt, and G.S. David, "Low molecular weight mercaptoethanol sensitive antibody in rabbits," Immunochemistry, 6: 649, 1969; J.W. Prahl, W.J. Mandy, G.S. David, M.W. Steward, and C.W. Todd, "Participation of allotypic markers in rabbit imunoglobulin classes," pp. 125-130 in Protides of the Biological Fluids, Vo. 17, ed. H. Pectors, Oxford: Pergamon Press, 1970.

approach toward the direction of work in his lab: "Charlie was a great manager. If you came up with an idea, it was never a response like 'no, that won't work,' or 'how are you going to do it?' His response was always 'OK, what do you need?' And that was a very enjoyable and nicely reinforcing way to manage a group, one you don't find too often." Todd's attitude toward organizing, supervising, and participating in scientific work rubbed off on David, just as Nisonoff's similarly positive approach had influenced him at Illinois. His experiences with these two bosses shaped the manner in which he conducted his inquiries and interacted with colleagues, collaborators, and subordinates throughout his career. They were the starting point, too, for ideas that he developed about how best to foster innovation and a spirit of collegiality in laboratory cultures – ideas that were later given concrete expression in the management style for which he became known and respected when he became a chief scientist and supervisor of many research teams at Hybritech.

David was content with his situation at City of Hope. He enjoyed working with Charlie Todd, and found no lack of interesting scientific projects with which to get involved. In addition to the immunogenetics experiments, he recalls, "there were always other things to play with up there that were more immunochemistry-oriented." Still, in the middle of his second year, he received an offer that he felt like he couldn't refuse – an invitation to take a staff position at the Salk Institute for Biological Studies in La Jolla, just north of San Diego. He decided to make the move as soon as possible. Two factors were paramount in his mind as he briefly mulled his options. The first was the world class reputation of the Salk Institute. "Nobody in his right mind," David reasoned, "would pass up an opportunity to go down to Salk." The second,

perhaps equally important factor, was what David perceived to be the higher quality of life in San Diego. He was eager to trade the heat, smog, and increasing congestion of the San Gabriel Valley for La Jolla's relaxed pace and cool ocean breezes: "When you're sitting up in the Duarte-Pasadena area, there's something enticing about San Diego." So, instead of sticking around City of Hope for the full tenure of his fellowship, he headed down the freeway to San Diego County, to work for Jonas Salk and lend his biochemical expertise to a project in tumor immunology. He started in his new job shortly after January 1, 1970. David tells of the odd way in which the move came about:

> There was an Australian chap named Sam who came into the Salk Institute. He had convinced Jonas that he could cure cancer. This was very provocative to Jonas. Sam somewhere got it into his mind that he needed someone to run the immunochemistry side of the lab who had come out of Al Nisonoff's lab. Well, there were only three Ph.D.s that had ever come out of Al's lab. He just got it into his head. Al was a damn good immunochemist. He had published a lot and done very good work, and the idea was that someone who had come out of that lab would be a good person to have. So, Sam tracked me down up at City of Hope and invited me down to Salk.

Sam's project was based on the speculation that cancers are permitted to grow when soluble antibodies inhibit the rejection of tumor cells by the cell-mediated immune response. His theory proposed, in effect, that, in the case of cancer, humoral immunity interferes with cellular immunity and prevents various components of the body's cell-mediated defenses (e.g. macrophages, T cells, NK cells, cytokines, and complement proteins) from doing what they would otherwise do naturally – round up, neutralize, and destroy rogue cancer cells. Sam conceptualized cancer as an immune deficiency, of sorts, as a systemic condition rather than just a cellular or genetic one.

This general view is now popular among cancer researchers. Many biomedical scientists are presently searching for ways to trigger effective immune responses to malignancies.[38] But Sam's specific ideas about the biological functions of antibodies, and, in particular, their roles in immune effector mechanisms, were unorthodox, as was the experimental therapy he intended to develop and test. It was Sam's plan to devise some means of eliminating the inhibiting factor – offending immunoglobulins – from cancer-ridden bodies. David explains: "The intent was to develop an excorporeal circulation method of removing the anti-tumor antibodies, or all Ig, from a cancer patient's blood."

David's work as a technician on this project set him on a scientific course that would prepare him well for many of the challenging tasks he would confront later when hired by Hybritech to work with monoclonal antibodies. He would become an expert in immunoassays and antibody technologies. In Sam's project, the goal was to remove blood from the bodies of cancer patients, extract immune inhibiting immunoglobulins from it, and return it to the patients. David set to work to develop a method of circulating blood through an immunoadsorbent employing anti-human IgG derived from sheep. The human antibodies were to be separated from the blood by binding with the anti-human sheep antibodies stabilized on the adsorbent. The blood cells and other blood components would then be recovered and the plasma, sans immunoglobulin, would be re-administered to the patient. Very large quantities of sheep antibody were needed – kilograms. Conventional methods of antibody

[38] For a recent overview, see Amy Adams, "Cancer Immunotherapy Inches Forward," The Scientist 18, 14, July 19, 2004.

production could not efficiently produce yields of this size. As an alternative, Sam envisioned a system for milking large amounts of fluid from sheep immunized against human immunoglobulins. This involved putting sheep on lymphatic pumps that constantly drained the lymph. The lymphatic fluid would then also be run through an adsorbent, from which, Sam hoped, large volumes of anti-human sheep Ig could be collected. David worked on the two immunoadsorbent systems for over a year, and gained valuable practical experience working with antibodies as tools, but, ultimately, the technology "was not something that really panned out." In addition to technical difficulties, Sam's ambitious project was beset by administrative and political troubles, and eventually ground to a halt. In the fall of 1972, David was ready to make an exit.

The young man was at an awkward point in his career. On the one hand, he had completed a Ph.D. under the tutelage of a world renowned chemist, he had on his curriculum vita stops at two prestigious houses of research – City of Hope and the Salk Institute, and he was known to collaborators and local colleagues as a smart, careful scientist, a sound technician whose work consistently met the highest standards of analytical rigor. Yet, he had only three minor publications to his name – reports on the rabbit experiments conducted with Charlie Todd. "One of my faults," he says, "is that publication has rarely been an interest to me. My interest was in understanding the stuff, not in telling everybody else what I had done, which is a little bit selfish, because one of the purposes of publishing, the real purpose that should be behind publishing, is teaching other people." But David didn't hoard data or withhold information. He wasn't secretive. He didn't play his cards close to the vest in order to

secure some advantage against competitors. He enjoyed scientific collaboration and was eager to make contributions to the larger collective enterprise and community of scientists. He simply didn't measure personal success by conventional means. He had little regard for status honor or formal professional advancement. While the emergence of biomedical 'big science' after World War II put increasing pressure on scientists to behave as bureaucrats, some resisted and adopted 'purer' artisanal approaches to their work. Gary David was one of them, a craftsman who was satisfied just to be in the laboratory doing good science.

In reviewing his career and telling of disappointments in scientific and technological projects that, by all outward appearances, came to naught and were judged failures, David invariably adds 'but we learned a lot.' His disinterest in and neglect of publishing as young researcher reflected his commitment to learning rather than a lack of effort or productivity. There was more than a bit of Max Gottlieb or Martin Arrowsmith – Sinclair Lewis' scientific idealists – in Gary David. He eschewed self-promotion. In the laboratory, experience and understanding were always his prime objectives. Rewards extrinsic to the work itself were secondary concerns. David was curious, engrossed by scientific work, dedicated to the acquisition of knowledge. He was interested in learning about the nature of things, to the extent that the sciences and human beings can discern it. But he wasn't much interested in plotting a career path. He didn't make all the right moves to establish himself as an independent investigator and lab chief in a university or academic research institute. He couldn't bring himself to play the academic game in anything more than a lackadaisical, half-hearted manner. David recognized that he wasn't

getting ahead in it, but he didn't care enough to change his habits. His approach, apparently, was to accumulate enough informal professional credit to enable him to continue doing high level scientific work. However, after administrative controversies and infighting had made his time at the Salk decidedly unpleasant toward the end, his ambivalence toward the social organization of academic research and his loathing of academic politics deepened. He began to sense that while he loved doing science and felt quite at home in laboratories, he was bound to experience a good deal of discomfort in scientific institutions.

Still, David never entertained the notion of giving up science, and, for the moment, didn't seriously consider moving into applied research in an industrial setting, either. He wanted to satisfy his curiosity, to follow his muse where it would lead him. "At that time," he says, "there was certainly no thought of anything but the academic life." David believes that his thinking about industry was colored by his knowledge of Al Nisonoff's experience. His mentor at Illinois had worked in industry as a chemist for U.S. Rubber, and had developed a very valuable process for adhering nylon cord to rubber; the technique led to the manufacture of nylon-belted tires, but he was ultimately dissatisfied with the work. Nisonoff wanted to do basic research. He wasn't able to pursue it at U.S. Rubber, so he returned to academia.[39] Early in his career, David was likewise chasing down interesting scientific opportunities, so, for him, "there was no consideration of anything but the academic community." This was before the advent of biotechnology, however. Biotechnologies would soon reshape

[39] See Rutgers University, New Brunswick, History Department: Oral History Archives of WW II; "Interview with Alfred Nisonoff," August 1, 1994.; transcript by Peter Wasek , Jennifer Lenkiewicz, and G. Kurt Piehler; http://fas-history.rutgers.edu/oralhistory/Interviews/nisonoff_alfred.html.

the landscape of opportunities and choices available to life scientists, and Gary David, the third employee hired at Hybritech, would take advantage of the expanded range of options. In doing so, he would participate in the creation of the hybrid culture that, in part, defined the field of biotechnology, and distinguished it from both academic life science research and industrial research conducted in the health care industry. And, in managing scientific work at Hybritech, David would draw on his background in academic labs and institutions, and on his thinking regarding what was both good and bad in them.

In the fall of 1972, all of this was part of an unforeseeable future. For the moment, David was thinking about managing only himself, improving his situation, getting away from the discord and politics at the Salk, and finding scientific work that would engage him. He was less concerned with where exactly that work would be done, or what exactly it would entail. "I think by that time," he says, "I had learned that there are a lot of interesting things to do." David started writing grant proposals to fund contemplated projects of his own, and he then contacted an old friend, Ralph Reisfeld, an immunologist who happened to be a faculty member down the street at the Scripps Clinic and Research Foundation. Reisfeld had spent a sabbatical year at Nisonoff's lab in Illinois when David was a graduate student there. Contacting him was the extent of David's job search activities in 1972. "Ralph had an opening and I was desperate to get out of Salk, so I went over there...it was just 'Hey, Ralph, I'm ready to leave Salk. You said a while back that if I ever decided to leave, to give you a call. I'm giving you a call.' That was pretty much the way it was." David was offered and accepted a position as an assistant in the Department of Experimental

Pathology at Scripps. He anticipated that it would be a stimulating environment because "Scripps had a very good reputation, there were very good people there, and it was a good place to go through."

David was awarded a grant for a project of his own, an exploration of cell surface antigens on tumor cells in a rat model, and, thanks to Reisfeld, he had a place to do it. Reisfeld had a similar project for David to work on, in addition. Reisfeld had been contracted by the National Cancer Institute to investigate the relationship between a specific antigen, a carcinoembryonic antigen – one of the polypeptides that appear on colorectal cancer cells but not normal cells, or are more plentiful on cancer cells – and the progression of tumor systems.[40] He was selected for the contract, David explains, because "Ralph was a histocompatibility antigen person, he had done a lot of work in cell surface antigens and things, and also because he knew a lot of people at NIH."[41] Reisfeld handed over the project to him, David says, because he "really didn't have anybody else to run it." Reisfeld knew him, and knew that he was qualified by virtue of his training and experience in immunology and biochemistry to manage the research. David wasn't entirely pleased with the way the project was conceptualized. The stated intent of the contract was to identify subsets (i.e., different molecular species) of the antigen that were diagnostic for colorectal tumors. David didn't see the point in identifying CEA subsets: "I always thought that was backwards.

---

[40] Carcinoembryonic antigens also appear in embryonic tissues, hence the name.

[41] The major histocompatiblity complex (MHC) is a cluster of genes (with allelic variations numbering in the hundreds) that encode for proteins (some of which bind carbohydrates and become glycoprotein complexes) situated on cell surfaces. MHC molecules are markers of cell identity – the immune system relies on them in processes of self/nonself recognition. In addition, MHC molecules on immune system cells play important signaling and activation roles in immune responses by combining with and 'presenting' antigens (i.e., making them visible and available to other immune system components).

To date, nobody has done it. In fact, it's far more valuable to identify the general class of antigen so that you can follow progression or regression of tumors that are expressing antigens." In any case, David took on the project, his reservations concerning its underlying logic notwithstanding, while simultaneously conducting his own research: "I spent the next six years between those two, between my grants and the contract. Most of my, effort, though, was spent on the contract. There was a lot more pressure to do that."

RADIOIMMUNOASSAY

David's work at Scripps could hardly have been a better preparation for the challenging technical tasks that he would later take on at Hybritech. He was working with antigens and antibodies, deepening his familiarity with their characteristics and behaviors, thinking about what could be done with them, and putting his ideas to the test. He was employing radioimmunoassays to do it. Immunoassays rely on antigen-antibody interactions to determine the presence or concentration of an immunogenic analyte in a sample.[42] The sensitivity and nearly universal applicability of antibodies as probes for biological substances have made immunoassay techniques prized tools of choice in numerous scientific, medical, and industrial fields. In radioimmunoassays, radioisotopes (usually a form of radioiodine) are linked covalently to either antigens or

[42] There are many different immunoassay formats, and many different techniques of separation and analysis are used to determine the results of the procedures (e.g., visual inspection, electrophoresis, autoradiography, chromatography, scintillation counting, nephelometry, turbidimetry, luminometry, etc.), but the formation of antigen-antibody complexes is common to all as the basis for analyte detection and measurement. See James P. Gosling, "A Decade of Development in Immunoassay Methodology," Clinical Chemistry, 36, 8: 1406-1427, 1990; James P. Gosling and Lawrence V. Basso, eds., Immunoassay: Laboratory Analysis and Clinical Application, Boston: Butterworth-Heinemann, 1994; Christopher Price and David J. Newman, eds., Principles and Practice of Immunoassay, New York: Stockton Press, 1991; Wild, David, ed., The Immunoassay Handbook, 2nd ed., London: Nature Publishing Group, 2001.

antibodies as tracers.[43] After bound and tagged antigen-antibody complexes are separated from unbound tags, emissions from the isotopes are read by means of radioautography or scintillation counters to signal binding activity.[44] (Other immunoassays employ enzymatic, fluorescent, chemoluminescent, or bioluminescent labels for the same purpose). Radioimmunassays were first developed in the late 1950s by Rosalyn Yalow, a nuclear physicist, and Solomon Berson, an internist, at the Veteran's Administration Hospital in the Bronx.

The initial discovery of the technique was fortuitous.[45] Yalow and Berson were studying diabetes. Medical researcher Arthur Mirsky had earlier proposed that the proximate cause of adult-onset diabetes was perhaps not a reduced capacity of beta cells in the pancreas to manufacture and secrete insulin, but rather the destruction of insulin in the liver by hepatic insulinase.[46] To test the hypothesis, Yalow and Berson followed the in vivo distribution and metabolism of radioiodinated insulin – hormone labeled with ^{131}I. They found that the conjugated hormone cleared more rapidly from non-diabetic controls who had never received exogenous insulin. The finding was not only contrary to Mirsky's hypothesis; it was also surprising (no significant difference

---

[43] ^{125}I is the typically preferred radioisotope because it binds easily to tyrosine residues on antigens and antibodies, its emissions can be recorded by a standard gamma counter, and it has a relatively short half-life – only sixty days. (The short half-life also means a short shelf. ^{125}I must be restocked every sixty days). See Rebecca Krumm, "Radioimmunoassay: A Proven Performer in the BioLab," The Scientist 1994, 8, 10: 17.

[44] Radioautography involves exposing photographic emulsion paper to radioactivity. Scintillation counters are photosensitive devices that detect low-level beta or gamma radiation.

[45] See Louis Rosenfeld, "Radioimmunoassay," ch. 10 in Origins of Clinical Chemistry: The Evolution of Protein Analysis, New York: Academic Press, 1982; Yalow, Rosalyn S., "Radioimmunoassay: A Probe for Fine Structure of Biologic Systems," Nobel Lecture, December 8, 1977.

[46] I.A. Mirsky, "The etiology of diabetes mellitus in man," Recent Progress in Hormone Research, 7: 437, 1952.

in clearance times would have been the expected disconfirmation of the hypothesis). Yalow and Berson concluded that the radiolabeled insulin had been bound by antibodies generated in response to previous administrations of the hormone, and that the physical chemical properties of the isotope-insulin-antibody complex made it more difficult to metabolize than unlabeled and/or unbound insulin.

The pair submitted an article to Science in 1956, but it was rejected.[47] Reviewing immunologists were not satisfied that the data were sufficient to support Yalow and Berson's postulation of antibody activity. The authors had analyzed the composition of their solutions by means of paper electrophoresis.[48] The migration across the paper of labeled hormone from patient samples when current was applied and the lack of mobility in labeled hormone from control samples indicated to them the presence of charged antibody proteins. But in the mid-1950s, before the broad acceptance of Burnet's clonal selection theory, immunologists weren't generally convinced that insulin was immunogenic, and they weren't prepared to accept electrophoretic indications of molecular weight and charge as evidence of antibody activity. Existing immunologic assays relied mainly on precipitation and agglutination. Unfortunately, the concentrations of antibody that Yalow and Berson wanted to identify were too low to be detected by these relatively insensitive methods.

---

[47] The paper was eventually accepted by the Journal of Clinical Investigation, after revisions, including deletion of references to 'insulin antibody.' See S.A. Berson, R.S. Yalow, A. Bauman, M.A. Rothschild and K. Newerly, "Insulin-^{131}I Metabolism in Human Subjects: Demonstration of Insulin Binding Globulin in the Circulation of Insulin-Treated Subjects," Journal of Clinical Investigation 35: 170-190, 1956; Rosalyn S. Yalow, "Radioimmunoassay: A Probe for Fine Structure of Biologic Systems," Nobel Lecture, December 8, 1977.

[48] S.A. Berson and R.S. Yalow, "Kinetics of reaction between insulin and insulin-binding antibody," Journal of Clinical Investigation 36: 873, 1957.

But without confirmation by some standard procedure for establishing the identity of antibodies, experts in the field of immunology – to which neither Yalow nor Berson formally belonged by training or institutional affiliation – were reluctant to concede that the experiment demonstrated immunoglobulin binding.

The first radioimmunoassay came out of further efforts by Yalow and Berson to establish their claim and explore its implications.[49] The original procedure was what has come to be known as a 'limited reagent,' or competitive assay. The validity of competitive assays is dependent on the identical immunologic behavior of antigen (and, specifically, its antibody binding characteristics) in unknown samples with antigen in known samples. So, in order to profile the immunogenicity of exogenous insulin, Yalow and Berson acquainted themselves with the behavior of insulin in a series of known samples. They again labeled various, definite amounts of the hormone with ^{131}I. They combined these quantities in solution with purified antibody taken from diabetics 'immunized' (medicated) with insulin. Finally, they employed autoradiographic techniques to measure emissions from the isotopic labels attached to the bound hormone-antibody complexes that resulted. These experiments enabled Yalow and Berson to plot a curve of standard responses of insulin to homologous antibody.

---

[49] S.A. Berson and R.S. Yalow, "Isotopic tracers in the study of diabetes," pp. 349-430 in Advances in Biological and Medical Physics, New York: Academic Press, 1958; "Quantitative aspects of reaction between insulin and insulin-binding antibody," Journal of Clinical Investigation 38: 1996-2016, 1959; R.S. Yalow and S.A. Berson, "Assay of plasma insulin in human subjects by immunological methods," Nature 184: 1648-1649, 1959; "Immunoassay of endogenous plasma insulin in man," Journal of Clinical Investigations, 39: 1157-1175, 1960.

The researchers were now prepared to perform immunoassays to detect insulin in unknown samples. They once more combined definite amounts of labeled hormone in solutions containing precisely controlled quantities of antibody. Now, however, they added specimens from immunized patients that contained undetermined amounts of unlabeled insulin. If Yalow and Berson's speculations were correct, the unlabeled hormone would compete with the labeled hormone for opportunities to bind with the limited amount of available antibody. They expected to see inhibited binding of labeled antibody, and they did. Electrophoresis was employed to separate bound and unbound labeled hormone, and planimetric comparisons of autoradiographic evidence (indicating ratios between radio emissions from bound and unbounded labeled hormone in tests of specimens and the same ratios in the tests undertaken previously in order to establish standards) were made.[50] Differences between a particular test result and the corresponding benchmark indicated degrees of inhibition and, simultaneously, the concentration of unlabeled hormone. Yalow and Berson realized that they had invented a sensitive method for detecting immunogenic analytes of all kinds at minute levels, and soon others did, too. In 1977, Yalow was awarded the Nobel prize in Physiology and Medicine. (Berson died prematurely in 1972.)

In her Nobel lecture, Yalow remarked: "My crystal ball – or intuition – tells me that in the 1980s the impact of RIA [radioimmunoassay] on the study of infectious diseases may prove as revolutionary as its impact on endocrinology in the 1960s."[51]

---

[50] Planimetry is the measurement of plane areas, or areas under a curve.

[51] Rosalyn S. Yalow, "Radioimmunoassay: A Probe for Fine Structure of Biologic Systems," Nobel Lecture, December 8, 1977.

She was correct, and, if anything, too conservative in her forecasting. Infectious pathogens constituted just a subset of antigens that researchers were investigating or detecting with radioimmunoassays. By December of 1977, when Yalow made her speech, radioimmunoassays had already become routine procedures in academic life science, medical schools and research institutes, hospitals, clinical laboratories, and the pharmaceutical industry. Many diagnostics companies were selling, or preparing to sell, RIA kits for the detection of a wide array of immunogenic substances and haptens (small molecules that bind with antibodies, but do not elicit immune responses) to users in these markets. And from the time the first radioimmunoassay protocols were published in 1960,[52] and researchers began to tinker with the tests and adapt them to new applications, RIA designs began to evolve and proliferate.[53] By the 1970s, there were many different ways to perform radioimmunoassays.

Several new formats, including tests known as IRMAs (immunoradiometric assays), gained widespread popularity after their introduction. The IRMA designation was employed to distinguish the format from competitive assays, like Yalow and Berson's, that employed labeled antigens. In contrast to standard RIAs, IRMAs call for antibodies to be labeled rather than antigens, and to be used at high concentrations. In standard RIAs, an unknown amount of unlabeled analyte in a sample competes with a restricted amount of labeled analyte for opportunities to bind with a restricted

---

[52] R.P. Ekins, "The estimation of thyroxine in human plasma by an electrophoretic technique," Clinica Chimica Acta, 5: 543, 1960; R.S. Yalow and S.A. Berson, "Immunoassay of endogenousplasma insulin in man," Journal of Clinical Investigations, 39: 1157-1175, 1960.

[53] The trend continues today. Since the mid-1980s, immunoassay developers have sought to move away from reliance on radioisotopic labels. Work with low-level radioactive materials requires the observance of special safety protocols and costly, inconvenient provisions for transportation, storage,

amount of free antibody in solution. In IRMA protocols, the idea is to use reagents in excess. High concentrations of labeled antibody increase the chances of binding all the analyte in a sample, thereby increasing the assay's 'signal-to-noise' ratio, lowering the sensitivity threshold and the capacity of the test to detect analytes in minute amounts.

The quantitative analyses performed in 'excess reagent' tests rely on different measurements and different separation techniques than those in 'limited reagent' tests (and so, are subject to bias and error from different sources). In standard RIAs, the analysis is comparative and is preceded by the separation of antibody-bound labeled antigen from free labeled antigen. In IRMAs, the required step involves separating antigen-bound labels (i.e., those attached to antigen-antibody complexes) from free labeled antibodies. In the theoretically ideal case, all antigen is bound due to the reagent excess, and radioisotopic emissions from labeled antigen-antibody complexes are therefore direct indicators of the concentration of the analyte present in the sample. The excess reagent approach makes IRMAs less dependent on antibody affinity for the antigenic target, but it also renders them more susceptible to imprecision due to non-specific binding. Non-specific binding refers to undesired and uncontrolled chemical or physical interactions of antibody or antigen reagents with any of the various elements of a test (e.g., components of the biological matrices – blood, serum, plasma, urine, etc. – in which the assay is performed, or equipment used to conduct the test – glass, plastic, adsorbent materials, etc.).

---

and disposal. Radioisotopes are also expensive and short-lived on the shelf. More automation and fast homogenous (one-step) assays are other trends in the field.

The earliest IRMAs utilized separation methods employed in standard RIAs (e.g., chromatography, electrophoresis, adsorption by charcoal, ion-exchange resins, or hydroxypatite, and fractional precipitation of immune-complexes in solution with ethanol, polyethylene glycol, dextran, ammonium sulphate, or sodium sulphate), and were plagued by high rates of non-specific binding – in the 10%-20% range. Reducing these rates and generating greater robustness in IRMA designs required gains in reagent specificity, more effective separation techniques, and greater control, generally, over chemical reactions in the assays. Assay technologists worked to develop systems that would deliver these gains, along with improvements in terms of speed, convenience, and cost-effectiveness, which could be realized by curtailing the duration of chemical reactions and incubations, eliminating unnecessary procedural steps, and making more efficient use of expensive reagents. An important advance in the field that afforded some of these advantages was the invention of the solid phase, double antibody (or 'sandwich') assay. The first IRMA of this sort was invented in 1969.[54] In standard RIAs, actual physical separations of bound and unbound labels are accomplished by some combination of filtration, adsorption, precipitation, or centrifugation methods. Double antibody, solid phase assays utilize a very different separation technique, one that significantly alters the characteristics of the labeled antibody-antigen immunoaggregate in order to make processing more manageable and consistent. Immune complexes in solid phase tests are considerably larger, and they

[54] S.W. Salmon, G. Mackey, and H.H. Fundenberg, "'Sandwich' solid phase radioimmunoassay for the quantitative determination of human immunoglobulins," Immunology 1969, 103: 129. See also, L. Wide, "Solid phase antigen-antibody systems," pp. 405-416 in Radioimmunoassay Methods, K.E. Kirkham and W.M. Hunter, eds., Edinburgh: Churchill Livingstone, 1971.

typically display greater stability and durability than those formed in liquid phase reactions.

Two different species of imunoglobulin are used in double antibody, solid phase formats. Each recognizes a different epitope, i.e., a specific antigenic polypeptide or glycoprotein, on the surface of the target molecule. In a generic assay design, one antibody is attached, or applied as a coat, unlabeled, to a 'solid phase,' a material substrate (many different materials have been used, including, for example, beads of various compositions and sizes, glass fibers, nylon membranes, polystyrene tubes, and microtiter plates). The first antibody binds the antigen at one epitope, immobilizing it on the solid phase. The second, labeled antibody is then added to bind the antigen at a different, unoccupied site on the antigen molecule. The final result is a labeled antibody-antigen-antibody precipitate (or sandwich) bound to the solid carrier. A wash completes the separation of bound label from free. Generally, solid phase methods produce separations that are more thorough and reliable than liquid phase precipitations can deliver.[55] They feature greater sensitivity, accuracy, and precision, usually without compromising speed, convenience, or consistency. Eventually, solid phase tests became favored for most purposes in most academic, medical, and industrial venues. By 1990, over seventy percent of new immunoassays incorporated solid phase separation technologies.[56]

---

[55] 'Homogeneous' or 'one-step' assays eliminate separation procedures. They offer the advantages of greater speed and convenience and but usually at the expense of sensitivity and accuracy. For certain purposes, they may be preferred; for others, not. They are generally unsuitable for the detection of analytes in the picofemtomolar (very low) concentration range. See Christopher Price and David J. Newman, Principles and Practice of Immunoassay, New York: Stockton Press, 1991, ch. 4.

[56] James P. Gosling, "A decade of development in immunoassay methodology," Clinical Chemistry 36, 8: 1408-1427, 1990.

THE RIGHT MAN FOR THE JOB

When Gary David left the Salk Institute for the Scripps Clinic and Research Foundation in 1972, radioimmunoassays had already become standard tools of the academic life science trade. They were routinely employed on Ralph Reisfeld's benches in the Department of Experimental Pathology at Scripps, and when David arrived there, he naturally adopted them, too. He immediately started using radioimmunoassays to study antigenic molecules associated with colon cancer, with the ultimate aim of developing reliable diagnostic tests for the disease. A paper that David co-authored with Reisfeld, along with Bob Wang and Dale Sevier (colleagues and friends whom David hired into Reisfeld's lab, and whom he would later recruit to Hybritech), identified this endpoint as the practical goal of Reisfeld's National Cancer Institute research contract: "It is our aim to render the CEA radioimmunoassay specific for the early detection of gastrointestinal tumors."[57] Two years later, another publication presented the group's dismal opinion of the current state of colon cancer diagnostics, but also asserted confidently that improvements would be realized through advances in radioimmunoassay methodology: "Although it may be years before assays are sufficiently refined to provide procedures capable of the detection and precise diagnosis of gastrointestinal cancer, we may expect to approach this goal by improving the reagents and methods."[58]

---

[57] R.A. Reisfeld, G.S. David, R. Wang, T. Chino, and E.D. Sevier, "New approaches for the isolation of carcinoembryonic antigens (CEA) and their utilization as immunodiagnostic reagents," pp. 487-498 in Cellular Membranes and Tumor Cell Behavior, Baltimore: Williams and Wilkins, 1975.

[58] R. Wang, E.D. Sevier, R.A. Reisfeld, and G.S. David, "Semi-automatic solid phase radioimmunoassay for carcinoembryonic antigen," Journal of Immunological Methods 18: 157-164, 1977.

So, most of the work that David carried out in Reisfeld's laboratory from 1972 to 1977 was devoted to improving radioimmunoassay technologies. He and his team encountered numerous technical difficulties in their studies of tumor antigens, and the toolbox for overcoming these obstacles was not well stocked. Immunoassays were the most effective means available for identifying and characterizing antigens, but the current state-of-the-art in the field left much to be desired. The procedures were touchy, complicated, and time-consuming. A great deal of skill was required to keep them running smoothly and to extract from them accurate and reliable results. As Bob Wang describes, achieving consistency in radioimmunoassay performance was a challenge:

> Doing radioimmunoassays, you rely on an immunoprecipitation reaction and association to occur, and what happens is, sometimes you don't add the second antibody right, or you've made a wrong dilution and you don't get a precipitation or you may get incomplete precipitation. Then, you've got to centrifuge it hard, with a lot of G force, to bring down the precipitate, because it's a fluffy precipitate. You've got to compact it at the bottom, and then you've got to wash it a few times, which means you've got to carefully decant off the supernatant, and then you've got to put some buffer in, and resuspend the pellet by agitating these microfuge tubes, and getting a good suspension so it's not just a clump and only the outside of the precipitate gets washed. There's a lot of potential for variation in the assays.

Naturally, given the practical difficulties that they confronted on a daily basis, David and the small team he had assembled under Reisfeld's banner closely followed developments in immunoassay design. The group was constantly searching for ways to improve their practices and to devise assays with greater reliability, precision, speed, and ease of use. They became aware of the advantages of solid phase tests shortly after the first assays of the class were invented and the protocols were

published. David was already familiar with solid phase technologies – he had found that carcinoembryonic antigens suffered significantly less chemical degradation if attached to solid phases before being subjected to purifying procedures that included filtering, freeze-drying, and baths in perchloric acid – and immediately understood the sense of working with antibodies in the same way.[59]

The new radioimmunoassay format was especially attractive to the Scripps researchers because CEA was difficult to radiolabel, and, in double antibody tests, immunoglobulins were labeled instead of antigens. Early solid phase assays typically conjugated antibodies to 'microbeads' – microcellulose particles – in order to facilitate and accelerate precipitation prior to centrifugation.[60] This is the format with which David and his team chose to experiment. They soon become very familiar with, not only its strengths, but also its weaknesses and limitations. As they learned how to work with solid phases, they developed strategies for managing or eliminating some of the format's problems and inefficiencies. Their efforts led to a series of methodological papers that announced new or refined methods for conjugating radioisotopes and proteins (antigens and antibodies),[61] culturing and maintaining supplies of antigen-bearing cells in vitro,[62] isolating, purifying, and treating various

---

[59] G.S. David and R.A. Reisfeld, "Solid state lactoperoxidase: a highly stable enzyme for simple, gentle iodination of proteins," Biochemical and Biophysical Research Communications 48: 464, 1972.

[60] Later solid phase formats featured much improved separation methods, and were able to dispense with centrifugation altogether.

[61] G.S. David, "Quality of radioiodine (Technical comment)," Science, 184: 1831, 1974; G.S. David and R.A. Reisfeld, "Protein iodination with solid state lactoperoxidase," Biochemistry 12: 1014, 1975.

[62] G.S. David and R.A Reisfeld, "Binding of carcinoembryonic antigen (CEA) to concanavalin A-sepharose: Storage of high-specific-activity ^{125}I-CEA," Journal of the National Cancer Institute, 53, 4: 1005-1010, 1974; G.S. David, R.A. Reisfeld, and T.H. Chino, "Continuous production of

biological and other materials as reagents, substrates, and adsorbents,[63] and analyzing the results of radioimmunoassays.[64]

Through the mid-1970s, David and his colleagues made several incremental improvements to the particular solid phase assay that they had adopted,[65] including the automation of the procedure. The fluctuations and inconsistencies of the test made it appear tempermental and capricious. Findings were difficult to replicate. One of three tests typically generated a result that was far out of line with the other two, so, for experimental purposes that didn't require a great deal of precision, the group ran the assays in triplicate and simply assumed that the correct value was something like the average of the two closest results. The process was laborious, and, according to Bob Wang, the members of the group shared "the basic trait of laziness." So, working from a model initially developed by Dale Sevier,[66] they adapted a cell harvester to

---

carcinoembryonic antigen in hollow fiber cell culture units: brief communication," Journal of the National Cancer Institute 60, 2: 303-306, 1978; R.A. Reisfeld, G.S. David, S. Ferone, M.A. Pelligrino, E.C. Holmes, "Approaches for the isolation of biologically functional tumor-associated antigens," Cancer Research 37, 8: 2860-2865, 1977.

[63] G.S. David, "Immunizations with immunoadsorbent-bound CEAs," pp. 599-602 in Onco-Developmental Gene Expression, ed. William Fishman and Stewart Sell, New York: Academic Press, 1976; R. Wang, E.D. Sevier, G.S. David, and R.A. Reisfeld, "An affinity adsorbent for the rapid purificaiton of wheat germ agglutin," Journal of Chromatography 114, 1: 223-226, 1975; R.A. Reisfeld, G.S. David, R. Wang, T. Chino, and E.D. Sevier, "New approaches for the isolation of carcinoembryonic antigens (CEA) and their utilization as immunodiagnostic reagents," pp. 487-498 in Cellular Membranes and Tumor Cell Behavior, Baltimore: Williams and Wilkins, 1975.

[64] K.A. Prescott and G.S. David, "The use of Polaroid Land Film in radioautographny," Analytical Biochemistry 57: 232, 1974.

[65] As a basic template for the particular methods they fashioned on their own, the Scripps researchers habitually cited a format described in F.C. Den Hollander, A.H.W.M. Schuurs, and H. van Hell, "Radioimmunoassays for human gonadotrophins and insulin employing a 'double-antibody solid-phase' technique," Journal of Immunological Methods 1,3:247-62, 1972.

[66] E.D. Sevier and R.A. Reisfeld, "Semi-automatic solid-phase double-antibody radioimmunoassay for β_2-microglobulin," Immunochemistry 13: 35-37, 1976.

wash and separate the beads and labels with a vacuum pump before counting in an automated gamma spectrometer.[67] They improved the throughput of the assay from 100 samples per week for one technician to 350 per day. The innovation was significant in the Hybritech story because the procedure later became the basis of the method that the company employed for many years to screen and select hybridoma clones of interest. But even with this substantial increase in efficiency, the researchers were not able to make a lot of headway in their cancer research.

The Scripps team had refined their assay system, but there were still many questions about carcinoembryonic antigens that they were unable to answer with the tools at hand. The accuracy and sensitivity of radioimmunoassays as probes of cancer cells were still limited by the properties of the reagents they employed, and especially the properties of antibodies. David and his colleagues came to know a lot about these properties. They learned many valuable lessons concerning how to treat immunoglobulins as hired hands. Working with antibodies as reagents in biochemical assays, and doing various things with and to them – isolating, purifying, labeling, precipitating, and centrifuging, for example – is difficult because, when placed under stress, an antibody is liable to become denatured, to unfold and lose its capacity to function in biological processes. When an antibody loses it shape, it is no longer able to bind antigens as it was designed by nature to do. Antibodies must be handled gently if they are to maintain their conformations. The Scripps researchers developed

[67] R. Wang, E.D. Sevier, R.A. Reisfeld, and G.S. David, "Semi-automatic solid phase radioimmunoassay for carcinoembryonic antigen," Journal of Immunological Methods 18: 157-164, 1977.

effective methods for preserving functional antibodies, eliciting their cooperation, and utilizing their labor power in experimental tasks.

One important limitation on radioimmunoassay performance that they could not overcome or significantly improve, however, was that imposed by the low specificity of polyclonal antibody mixtures. The research being conducted on Reisfeld's contract moved slowly because CEA is an antigen with a great deal of molecular heterogeneity. Colon cancer cells are diverse in structure. They feature many antigenic variations – differences in the precise molecular configurations of proteins that reside on their surfaces. The diversity problem was compounded by the harsh purification procedures to which antigens are subjected in preparation for immunizations. These treatments sometimes introduce further molecular alterations. Consequently, polyclonal antibody sera produced from immunizations to CEA display broad specificities. They contain many different antibodies that recognize many different antigenic targets. Immunoassays employing polyclonal antibodies lack the capacity for precise quantitative assessments of specific antigenic determinants.

Further, as antiserum becomes less specific, the potential for cross-reactivity – the interaction of antibodies with similar antigenic sites on different molecules and cells – increases. Cross-reactivity diminishes the accuracy of immunoassay results. In the case of colon cancer research, investigators had identified numerous CEA-like molecules derived from cells associated with different cancers and non-cancerous conditions. In the diagnostic immunoassays run by David's group, it was possible that the polyclonal antibody reagents were interacting with molecules of this kind. It was therefore impossible to gauge the accuracy of the tests. The lack of immune

specificity in polyclonal antibody sera prevented the researchers from sorting out all of the antigenic variances in CEA and all of the factors that may have been confounding their results. After conducting repeated tests that showed anti-CEA antibodies binding to CEA or CEA-like molecules in test samples, David and his colleagues were forced to concede that they were still unable to say "whether these anti-CEA reactive antigens are indeed CEA, antigens with share some determinants with CEA, or simply artifacts resulting from the immunological reagents utilized in the radioimmunoassy procedure."[68]

The inadequacy of polyclonal antibodies in the identification and characterization of antigenic molecules was soon to be remedied by hybridoma technology and the production of monoclonal antibodies. Monoclonal antibodies are 'exquisitely specific.' In addition to permitting reagent standardization, they vastly enhanced the capacities of immunoassays to clarify relationships among subspecies of heterogeneous antigens and to distinguish experimental artifacts. They also significantly reduced the problem of cross-reactivity. From late 1975, when Köhler and Milstein's announcement of hybridoma technology was published in Nature, through the middle of 1977, when Gary David was concluding his time at Scripps, a few immunologists scattered around the world, on the front lines of research in the field, were beginning to think about how to incorporate monoclonal antibodies into radioimmunoassays as reagents. It eventually became clear to those familiar with hybridoma technology that monoclonals would, for many purposes, become preferred

---

[68] R.A. Reisfeld, G.S. David, R. Wang, T. Chino, and E.D. Sevier, "New approaches for the isolation of carcinoembryonic antigens (CEA) and their utilization as immunodiagnostic reagents," pp. 487-498 in Cellular Membranes and Tumor Cell Behavior, Baltimore: Williams and Wilkins, 1975.

substitutes for less specific polyclonal mixtures in radioimunoassays.[69] Ivor Royston and Howard Birndorf, in residence at Stanford during this period, were among them (although they didn't consider going into the diagnostic immunoassay business until Brook Byers proposed the idea). The research that Gary David was conducting on colon cancer was similar in many respects to the work that Royston would soon begin on lymphoma and leukemia after moving to San Diego. Like Royston, David was well acquainted with the limitations of polyclonals, and, so, primed to recognize the utility of monoclonal antibodies when they entered his field of view.

In the middle of 1977, Gary David came once again to a crossroads in his scientific career. Reisfeld's NCI contract had expired. It had been renewed several times (even though at the height of the federal government's war on cancer, promises of practical medical benefits were often required to attract and sustain funding), but finally lapsed due to Reisfeld's lack of interest, the departures of Dale Sevier and Bob Wang, and the lack of substantive progress toward a reliable diagnostic test. David's own grant, supporting research on cancer antigens in rats, was renewed once, but not twice: "I had not put enough effort into it to get it renewed another time. I had kind of gotten interested in some other things." His last year at Scripps was devoted to other projects in immunology and protein chemistry.[70] For a time, he considered carrying

---

[69] This was an exclusive club, however. Few life scientists or medical researchers were familiar with hybridoma technology in 1977. Rosalyn Yalow, for example, in her 1977 Nobel lecture, talked at length about the numerous ends to which radioimmunoassays could likely be put in the future, but she made no mention of hybridoma technology or monoclonal antibodies.

[70] N.E. Harding, J. Ito, and G.S. David, "Identification of the protein firmly bound to the end of phage 129 DNA," Virology, 84: 279, 1978; G.S. David and C.M. Wiglesworth, "Target cell-substratum interaction. II. Complement dependent antibody induced inhibition of adherence," Journal of Immunology 119: 500, 1977; G.S. David and C.M. Wiglesworth, "Target cell-substratum interaction. I.

on much as he had been, stringing together grants and laboratory positions that would enable him to keep doing interesting scientific work. He wrote up a few grant proposals, hoping to attract support for new studies that he might conduct at Scripps:

> There were some calls out of NIH for more innovative grant applications. I had some ideas, so I wrote them up and submitted them. I got back the response and the score was not quite high enough to get funded. The response I got back was 'this is very interesting and it's very innovative' – which is what I thought they wanted – 'but what proof do you have that it will work?' And my reaction to that was, if I had any proof that it would work, I wouldn't be interested in doing it. That was about the time that I decided that my academic career had a finite lifetime.

With his best ideas shot down, David's funding situation became precarious. But while he was disenchanted with the clunky bureaucratic approach to fostering innovation, peer reviewers weren't the only source of frustration for him. His circumstances within Scripps had changed as well. Bob Wang and Dale Sevier, David's working partners had both resigned from Scripps (Wang in 1975; Sevier, the following year) to take jobs in industry, and David felt as if the local atmosphere was becoming toxic. He was assigned a new working space, when he would have much preferred to stay in his old location:

> Part of what kept me at Scripps so long was that, when I went to Scripps, there wasn't room in the main building, and I was given a lab in surg facilities behind Salk, the ones out on the cliff. I spent most of the six years there, and it was very nice. We had a nice little community of people who were kind of isolated from all of the political crap that went on at Scripps, and we learned a lot, we did good work, and it was a very enjoyable experience.

Effect of primed lymphocytes on a rat mammary adenocarcinoma tumor cell line," Immunological Communications 7: 337, 1978.

But the Salk Institute eventually asked Scripps to vacate the buildings. David's friendly, nurturing community was booted out and brought back on-site, into the main Scripps facility. That, he says, was "a second blow to an academic career." He wasn't happy to be back. He didn't care for the culture of the institution. The group out on the cliff had shared the same sentiments about the administration and the organizational climate. After the move, David felt like he had been deposited into "the middle of the egos and the politics that went on," and, he says, "I didn't like it." Bob Wang describes Scripps in the 1970s as a tense and conflicted environment:

> Talk about politics at Scripps.... The Research Foundation reorganized at the time into separate departments, including cellular immunology and molecular immunology, I believe. They all used to be experimental biology. You had biochemistry and microbiology, and those two departments were like poor step-sisters in the Research Foundation. There were a lot of politics among the senior investigators at Scripps, and you know, I'm sure it's still like that. It was a real Peyton Place, too. It was amazing how much the politics ruled in that place. They had a doctors' lunchroom, an M.D. lunchroom in the old Scripps Clinic. The Ph.D.s weren't allowed in there. This was a pretty nice lunchroom. M.D.s could go there, and M.D.s were more highly regarded than the Ph.D.s in the research organization, which is just bizarre. That was the mentality, and it probably still is pretty much today.[71]

This wasn't the kind of place in which Gary David could flourish, and he was only marginally attached to it. But he wasn't sure what to do next. He had been scientifically productive at Scripps, but he hadn't done much to establish a solid

---

[71] Wang adds: "I'd have to say a lot of medical doctors today are more qualified researchers because it's become more of a recognized specialty to be a research M.D. But back then, M.D.s learned by being put under fire, and were not as qualified as Ph.D.s." The preeminence of physicians in the institution had to do with the history of Scripps. The research arm evolved from the clinic, which had always been an elite medical facility providing services to an upscale clientele. Wang says, "I remember sitting in a research meeting, and out the window there's John Wayne in a bathrobe, looking like an old man, which he was, you know, getting a physical exam. And everybody's saying 'Oh, look. There's John Wayne.' So, it interrupts the research meeting and everybody looks out the window: 'It is John Wayne.'" The clinic has since opened it doors to welcome the hoi polloi.

academic career for himself, and the prospect of continuing as a vassal in embattled departmental fiefdoms held no appeal for him. For the first time, he began seriously to consider the route that his pals Wang and Sevier had traveled out of the academy. He began contemplating a move into industry. Wang had gone off to International Diagnostic Technologies, Inc., a Santa Clara start-up in the immunodiagnostics business. Sevier had taken a position as a research scientist at Biosciences, Inc., a reference laboratory in Van Nuys, California. Both were hired for their expertise in immunoassays. David recognized that he possessed the same marketable skills, and after his experiences at the Salk and Scripps, he was ready to look at industrial research in a new light. A friend put him in touch with a firm called Larson Diagnostics that was getting started in La Jolla.

David recalls: "Roger Larson was a mechanical engineer in Illinois who had invented something and had made a pile of money. He used the money to start the company." The firm was trying to develop a new diagnostics technology – fluorescence depolarization immunoassays. In this kind of assay, fluorescent molecules rather than radioisotopes are used as antibody tags. When illuminated with polarized light, they emit polarized photons. Emissions from bound and free labels can be distinguished by spectrometry because binding alters the behavior of fluorescent molecules; their motion is restricted and the photons they give off are 'depolarized.' Getting involved seemed to David like an opportunity to take up an interesting technical challenge, as well as a chance to get away from the frustrating politics of Scripps and the academic system. He worked on the project a bit, but pretty quickly ascertained that the technology wasn't going to be competitive: "It was not

there. The instrumentation is there now to do it right, but I think other things have come along that are still better, and it's not gotten a foothold." David perceived problems, in addition, at the business end of the Larson operation. "It was apparent," he says, "that it wasn't going anywhere, so I left."

By this time, it was 1978. Hybridoma technology was gradually diffusing beyond the discipline of immunology. David became aware of it, or began to think seriously about it, when he spoke with a friend in the San Diego scientific community, microbiologist David Kohne. At the time, Kohne was at UCSD, attempting to exploit nucleic acids as diagnostic probes. "We were talking, we were chatting, and I think Dave was very much of the opinion that hybridoma technology would have major implications in the diagnostics community, and it made a lot of sense to me, so I started thinking." David knew enough about immunodiagnostics to see that there would eventually be many commercial and technological opportunities created by the availability of monoclonal antibodies. He seized on a very modest one – one he thought he might be able to take advantage of by himself:

> The opportunity, really, was a little strange because it occurred to me that something people would need was a way to recognize, a way to separate out mouse monoclonal antibodies from ranch mixtures, in other words, anti-mouse IgG. Well, my wife had a horse that was going lame, and we didn't want to put it down. So, ah! What do you do with a horse that you don't want to put down? Well, maybe you can make a business out of it. I picked up a couple of goats, and immunized the horse and the goats with mouse IgG, and started a company around anti-mouse IgG. The idea was to get a little capital and use that to get into the monoclonal antibody business.

The company was called AB2, Inc. (for second antibodies). David did some of the work in his garage – he had a house on Poole Street near the university, an address

shared by hundreds of scientists since the La Jolla campus was established in the 1960s. He had, in addition, secured some lab space at the La Jolla Cancer Research Foundation not far away on North Torrey Pines Road. He was helping a group of post-docs there set up assays. The Foundation leased him the laboratory space in exchange for his consulting services. He remembers being approached by a stranger one day as he was working in the lab: "Howard Birndorf walked up to me and said, basically 'How would you like to join us?"' Birndorf had just moved into the building himself, to get Hybritech started. He was in need of an immunochemist and had somehow learned of David. Birndorf no longer remembers the details. He just says, "Somehow, through the grapevine, we heard about him." David suspects that it was Bill Fishman, the director of the Foundation, who gave Birndorf his name. In any case, the grapevine was not very long.

David was dismayed to learn that he already had competition in the monoclonal antibody business in San Diego, and that his competitors were already so far ahead of him. Unlike Royston and Birndorf, he didn't have myeloma cells, he didn't have money, and he didn't have an impressive record of publications, nor an established reputation as an independent investigator in science or medicine. And he probably didn't have the entrepreneurial moxie that Royston and Birndorf displayed, either. He had an old horse, access to a few antigens through his scientific connections, and a nose for technical challenges. As a proprietor, he was hopelessly overmatched. Still, during his years as a scientist in San Diego, he had become an expert in the care and feeding of antibodies and antigens, protein radiolabeling, and radioimmunoassay design, while expanding and enhancing his knowledge of antibody

chemistry and antigen-antibody interactions. He possessed a wealth of scientific experience and skill that made him the right man for the position that Howard Birndorf needed to fill. Birndorf recalls, "He was a really bright guy. He had the right background. He was in immunodiagnostics. He knew a lot about antibody assays, that kind of stuff." When Birndorf extended an offer, David didn't have to spend much time deliberating. "I had the option," he says, "of joining Hybritech or competing with Hybritech, and since there were about five or six orders of magnitude difference in capital, there wasn't much choice. So, that was how I got to Hybritech."

SOMEHOW, THROUGH THE GRAPEVINE

When David first went to work for the company, there wasn't much to it: "There were no labs at the time, no lab equipment, nothing. It was just a shell, just an idea." Howard Birndorf, the vice-president of everything, was there, sitting by himself, as he says, "in an empty office next to a bare lab with a desk, chair, telephone, and scientific catalogs." The company didn't yet have a functional laboratory. No technical operations had commenced, but the firm did have a scientific objective. The plan, as Royston had arranged with Tom Perkins, was to produce monoclonal antibodies against hepatitis B. The first step for the company was to figure out how to accomplish this goal. With the fourth quarter of 1978 ticking down, Birndorf and David began formulating an R&D program. Birndorf equipped the labs, set up an animal room, hired a few technical assistants, and then took a trip to the East coast to find hepatitis B surface antigens, with Brook Byers along as a chaperone. After being turned down by several different pharmaceutical companies, the pair finally secured antigen from non-profit sources – the CDC and WHO. In the process,

the company began establishing relationships with many different individuals and organizations, and not only those who agreed to supply resources in this particular instance: "There were a lot of people in the field who were interested in what we were doing." Birndorf and Byers were spreading the word. From these first discussions with people situated variously in science, medicine, and the diagnostics and pharmaceutical industries, the company eventually constructed a broad network of contacts.

Birndorf and David also began to collect different myeloma cell lines, so they could experiment with them, learn about their properties, and compare them. They wanted to find out, for example, which had the best fusion characteristics, which divided rapidly or grew slowly, and which generated the best antibodies, or yielded the largest quantity of useful or promising antibodies. There was no gold standard. The technology was brand new, and no one in the sciences or in industry had a clear idea of the best materials or best practices to employ in order to achieve any given end. "I know we got cell lines from several places," says David. "No two cell lines are the same once they've been split and carried in different labs. They end up having different characteristics. Everybody selects, intentionally or unintentionally, for different purposes." Birndorf and David started trying out the various lines they received to see which of them worked best. Initially, Birndorf did most of the cell biology work: "I did the first fusions myself. There was nobody else to do it." He took antigen prepared by David, immunized and sacrificed the mice, tended the murine lymphocytes and myeloma cells, hybridized them, and then cultured the hybridomas. From that point, the hybrids went to David for immunochemical

processing and analysis: "Once the animals started showing good titers, or reasonable titers, or acceptable titers, on our first target, hepatitis antigens, then it came time to really put everything together and do the fusions and the screens, and pick out the first clones, and try to isolate and characterize the antibodies." So, David's early contributions to the firm involved establishing methods and routines for preparing antigens, screening hybridomas and the monoclonal antibodies they secreted in order to find immunoglobulins suitable for specific antigens and specific purposes, and then, after returning selected cells to mice for incubation, separating and purifying supplies of antibody from ascites fluid by precipitation and column chromatography.

David boiled down the decision regarding a screening test to a choice between the assay that he had developed at Scripps with Dale Sevier and Bob Wang and an assay kit that Abbott had marketed for the detection of antibodies to hepatitis: "The real key at that point, as far as I was concerned, was to demonstrate – and I went into this with a bias – that the semi-automatic solid phase screening test [the Scripps test], as it became finally referred to, would do what we needed for the life of the game." The Abbott test was a solid phase assay for antibody, but it was too expensive, in David's view, and it was packaged with hepatitis antigen fixed on the solid phase (polystyrene beads) and reagents appropriate to hepatitis. Consequently, the assay chemistries would have to be reconfigured for every new antigen that the company wanted to investigate. David began working with his own test, the cellulose particle solid phase assay that he had helped to devise at Scripps, the one that he knew best. He found that, for the tasks at hand, "it was pretty clean. I don't remember any problems at all. It was pretty straightforward." So, David found that the Scripps

radioimmunoassay was an appropriate tool, and Hybritech did, in fact, use it to screen clones all the way through the mid-1990s.

When David began screening, he found that the first fusions had produced hybridomas secreting immunoglobulins specific to hepatitis B surface antigen. This immediate success was a bit unexpected, because, at the time, hybridoma technology was still very new and far from standardized. Scientists were still experimenting with it, still trying to discover and catalogue reliable rules of method. Failures were common and often inexplicable. It was not at all unusual for researchers to get wildly varying results from procedures performed in ways that appeared to be identical – several fusions in a row, for instance, would produce few functional hybrids, or perhaps none at all, while the next, for reasons unknown, might yield dozens. Birndorf was still experimenting with the process, too, but Hybritech got lucky on the first try. Royston says: "We succeeded in making the hepatitis antibodies in record time. I give Gary David a lot of credit for that, and the rest of the staff, but Gary was able to characterize the antibodies very quickly once they were produced." Just two months after getting started, Birndorf was able to report to Byers that the firm was already far ahead of schedule: "By December I had hired four or five people and completed the first proof of principle experiments making monoclonals to the hepatitis B antigen."[72] Gary David then went to work screening the clones, analyzing and comparing the immunoglobulins they produced, selecting the best among them, and culturing the cells that produced them. By February, 1979, the firm had its first prototype antibody product. According to Walt Desmond, a cell biologist from

UCSD, who came into the company some months later, that October to February antibody development was much faster than the subsequent efforts with which he was involved:

> There was a range. I remember, there were difficult and easy antigens. I would say that it was usually one to two years for getting the clones. That probably sped up as we learned more. I think we used to say, one to two years for getting the clones you wanted, and then maybe you would hope a year of product development [for an immunoassay kit]. So, two to three years for developing a product, from the beginning to the end. Now, it went much faster than that if you were just making a research antibody. I'd say one to two years for that. Some of them probably took three years.

With the proof of principle hurdle crossed, the company – comprised of Royston, Birndorf, Byers, and David, basically, at the time – started to think about expanding, about refining, coordinating, and scaling up the various processes that would lead to the manufacture of products and the generation of revenues from sales. More of all materials would be needed, of course – antigens, cells, mice, antibodies, laboratory supplies and equipment, space, and so on – but, in addition, Hybritech needed more people, and more people with specialized scientific skills. Ivor Royston and Howard Birndorf knew a lot about the cell biology end of things. Gary David brought with him expertise in immunochemistry. He knew a lot about antigens and antibodies and immunoassays. To grow, the company needed to find many more people like these three. In order to expand its operations, it needed more good scientists to conduct the research, refine the technology, and discover how to develop marketable diagnostic products with monoclonal antibodies. Fortunately, thanks to the scientific institutions in the area, a skilled labor force was readily available. Talk

---

[72] Quoted in Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, p. 51.

about what was going on at the new company began gradually to circulate through the local scientific community, and young researchers soon start to find their way to the company just as Gary David had – somehow, through the grapevine.

Walt Desmond says, "I first heard about [Hybritech] from a friend in the scientific community. That was Gary David. He had started working for them, and he called me up and said that I should take a look at this new company that they were starting." And once Desmond was in, he, too, started talking to friends and acquaintances. Greg Payne was twenty-three years old with a fresh bachelor's degree in biology from UCSD when he was hired by Hybritech as a lab technician. "One of my professors," he recalls, "said, 'I know some people who are starting up this little biotech company.' He knew Walt Desmond." Jeanne Dunham, Hybritech's first manufacturing person, was directed to the company by Bob Wang. In 1979, she was working for Calbiochem, a San Diego reagent manufacturer, and was passed over for a promotion. "I didn't get it," she says, "so I got angry." She was preparing to quit when she to spoke to Wang, who was also employed at the time by Calbiochem. Wang knew of Hybritech from Gary David, and would soon join the start-up himself. He told Dunham that he would get her an application. Dunham recalls the conversation: "I said, 'Hybritech? Never heard of them.' And he said, 'No, no, that's a good company.' So, he got me an application, I filled it out and interviewed with Howard, and got hired right away."

That's how it went. According to Desmond, everyone who came into the firm began recruiting, thinking about possible contacts with "people that we collaborated or worked with in the past." Scientific and technical positions at all levels (although, in

the beginning, the organizational hierarchy was not well-defined, and more horizontal than vertical) were filled mostly by people brought in from Scripps, the Salk Institute, and UCSD. Byers and Royston were on hand, conducting interviews, and, in fact, all of the scientists hired in the early days participated in the screening of new employees. Desmond remembers: "I was involved in all the interviews. We had kind of team interviews. A hundred lunches at Torrey Pines Inn, which was the only eating establishment in the area, over at the golf course. That was it. That's where you went to eat. And we were all thinking of people that we knew around town to recruit. That was a big effort."

Hybritech was off to fast start because it had two smart, enthusiastic, and persistent entrepreneurs. It also had access, through the entrepreneurs' social and professional contacts, to scarce but crucial resources – myeloma cells, hybridoma technology, and enough money to set up a scientific R&D program. Finally, the firm was able to attract highly skilled scientific personnel to staff the operation. As it did, it began to evolve organically. Of course, the venture capitalists at Kleiner-Perkins were in charge of corporate affairs, they dominated conversations about strategic direction, and they imposed financial discipline on the scientists. Provisional chains of command were established, financial projections were made, budgets were calculated, experimental programs were planned, schedules were drafted, and performance milestones were determined, but the organization wasn't built according to any blueprint. It just happened. New people came in and collectively transformed it, and made it into something unique. The company became a scientific organization quite unlike any of the other larger institutions surrounding it. Gary David was

pleased that, initially, at least, it seemed to lack the kind of political infighting that he found so distasteful at Salk and Scripps. He describes the character of the firm in the early days:

> It was quite different from working at Scripps. Because it was not an academic organization, because everybody was focused on one end, it turned out to be an extremely different culture. The goals were making the process work and the products come out. It was much more a real team effort, because we knew that we had to work together to make it happen, which even today, you rarely find in academic circles – you still find too much ego-derived, personal goal involvement. To me, that formation of the Hybritech culture was a wonderful learning experience. It was extremely valuable to see how rapidly science could progress when you were working with people instead of competing with your colleagues.

Many early participants have remarked on the distinctive character of the place. It made a lasting impression on Russ Curry, who was hired by Birndorf out of Ralph Reisfeld's laboratory at Scripps as Hybritech's first head of cell biology. Curry calls his time with Hybitech "one of the most interesting experiences I have had in my life. I was fascinated how the thing – the company – seemed to have a life of its own. The sum was greater than the parts." By his own account, Curry didn't fully understand how unusual was the culture at Hybritech until he acquired further experience in business, experience that allowed for comparisons:

> Many years later, I was recruited into an 'intrapreneurial' operation in a Fortune 50 company (one of the endless trends in big business, like 'reinventing the corporation,' and the other fad bullshit that keeps surfacing), and expected to enjoy the same experiences. There was a lot more money (as in millions rather than thousands) available, and lots of expensive travel, perks, etc., but it just wasn't the same....when that broke up, I ended up in the regular company environs and it was really regimented, really wasteful, and really stoopid [sic], in my

> estimation, which may explain why everything costs a lot more than it should.[73]

The evolution of Hybritech as an organization, a business, and a locus of scientific work, was a complex social process given its distinctiveness by the particular social and geographical context in which it took place – the various scientific institutions located in the northern suburbs of San Diego. Certainly, from a sociological point of view, the story of this evolution is not properly told as a tale of individual entrepreneurial or scientific achievements, although individuals, of course, played their parts. High-tech innovation is a team sport, and the roster of important participants in the entrepreneurial project at Hybritech grew rapidly as the company got underway. As this happened, the roles of the two original entrepreneurs diminished correspondingly. Of course, as chief operating officer and vice-president of everything, Howard Birndorf always had plenty to do, and Ivor Royston continued to keep track of what was going on, both in the laboratory and in the boardroom. By early 1979, however, a dozen other people were making crucial contributions to the success of the operation. The technical foundations of the firm – hybridoma and immunoassay technologies – were derived from the accumulated experience and wisdom of, not just the founders, but countless scientists who labored in many different scientific institutions and disciplines. And the direction of the company had already largely slipped out of the founders' hands. Less than a year before, in the spring of 1978, the company was just a private idea shared exclusively by Royston and Birndorf. They hadn't then envisioned anything like the ambitious project that had

[73] E-mail communication, August 28, 1997.

mushroomed beneath them in the ensuing months. Now, although the company had just gotten started, and had just hired its first employees, it was no longer really theirs. The pair provided valuable services to Hybritech, but they now did so as members of an organization, an institution, and an ongoing collective process that was being propelled forward by its own momentum.

VIII. A MAGICAL PLACE

> The prudent man may direct a state, but it is the enthusiast who regenerates it.
>
> Edward Bulwer-Lytton

ANTIGENS AND ANTIBODIES

Hybritech's first year was devoted largely to scientific exploration. The company worked to expand its scientific and technological capabilities, refine its production methods, and bring into the organization more scientific and technical personnel. Research efforts centered on purifying and characterizing new antigens and antibodies, and learning how to improve fusion, cloning, screening, culturing, and antibody harvesting processes. The R&D program was split into two arms – cell biology and immunochemistry – from the beginning, as Howard Birndorf and Gary David divided the firm's scientific labor between them according to their areas of expertise. When not engaged by the task of coordinating virtually everything that happened at the new company, Birndorf worked with cells – myelomas, lymphocytes, and hybrids. He maintained cultures and performed fusions. David worked with antigens and antibodies, and performed immunochemical assays to identify, analyze, and evaluate the monoclonal antibodies and immunoglobulin fragments secreted by the fused hybrids.

Russ Curry was soon lured from Ralph Reisfeld's lab at Scripps to take over existing cell biology chores from Birndorf, and to work on improving clonal expansion techniques – i.e., the stimulation of antibody generating cells in response to immunizations. (In the case of non-immunogenic substances, the immune system has

to be 'tricked' into generating antibodies; typically, this is accomplished by binding the target antigen to a known immunogen.) Curry was asked to develop methods for initiating or amplifying humoral immune responses. He was also handed the responsibility of overseeing inter-peritoneal injection and ascites fluid collection procedures in the company's vivarium (the animal room), where Balb/c mice served as living antibody factories. Curry was well qualified. He was a Ph.D. biologist from UC-Riverside. At Scripps, he had been employing somatic cell hybridization in studies of cellular genetics, so he knew all about Köhler and Milstein's work. Before moving across the street to Hybritech, he had become involved in the first successful hybridoma experiments at Scripps. Those experiments had produced monoclonals against T and B cell surface antigens.[1] He learned of Hybritech through the local grapevine, and through his acquaintance with Gary David.

Later in the year, Curry left, unconvinced that Hybritech would ever amount to anything significant. Royston, Birndorf, and Byers replaced him with Joanne Martinis, a cell biologist they recruited from the Wistar Institute in Philadelphia. The Wistar Institute had, like the Stanford University School of Medicine, benefited from Len Herzenberg's generosity with César Milstein's myeloma cell line, and, like Stanford, had become one of the few early homes of hybridoma technology in the U.S. in the late 1970s. After gaining access to Milstein's cells, three senior Wistar

---

[1] S. Ferrone, M.A. Pellegrino, M. Belvedere, R.A. Reisfeld, R. Curry, and J.P. Allison, "Human B cell antigens: Biological and immunogenic properties," pp. 645-655 in Protides of the Biological Fluids: 25th Colloquim 1977. Proteins and Related Subjects: Volume 25, Peters, H., ed., New York: Pergamon Press, 1978; R.A. Curry, V. Quaranta, M.A. Pellegrino, and S. Ferrone, "Serologically detectable human melanoma-associated antigens are not genetically linked to HLA-A and B antigens," Journal of Immunology 122, 1979: 2630-2632.

investigators, Hilary Koprowski, Carlo Croce, and Walter Gerhard retooled their labs for hybridoma research. Martinis worked under Croce as a postdoc, so she knew all about hybridomas and monoclonals. In June of 1977, Koprowski, Croce, and Gerhard filed a patent that broadly covered the production of monoclonal antibodies against viral antigens.[2] In May of 1979, Koprowski co-founded a monoclonal start-up called Centocor, in Philadelphia, with businessman Hubert Shoemaker. Like Hybritech, Centocor intended to develop diagnostic products. The firm began working on tests to detect CEA and rabies. Martinis didn't become involved with Centocor, but she was aware of it. She understood the commercial implications of hybridomas and monoclonals. The Hybritech people knew of her from the hybridoma literature.[3] Royston says she was "a really good cell biologist. She was an expert at cell hybridization." Others at the company have called her "a wizard" and "absolutely brilliant." She didn't immediately accept the invitation to join Hybritech. She was a serious East Coast academic with preconceived notions about the lack of gravity in

---

[2] Hilary Koprowski, Walter V. Gerhard, and Carlo M. Croce, "Process for providing viral antibodies by fusing a viral antibody producing cell and a myeloma cell to provide a fused cell hybrid culture and collecting viral antibodies," U.S. Patent 4,196,265, filed June 15, 1977; issued April 1, 1980. Alberto Cambrosio and Peter Keating note that the patent was widely ignored and infringed, apparently because it was widely believed that it wouldn't withstand a legal test and that, due to the expense of litigation, the Wistar Institute would not seek to enforce it. The patent did not prevent Hybritech from developing monoclonal antibodies against hepatitis. See Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, New York: Oxford University Press, 1995, p. 203, n 9.

[3] C.M. Croce, M. Shander, J. Martinis, L. Cicourel, G.G. D'Ancona, T.W. Dolby, and H. Koprowski, "Chromosomal location of the genes for human immunoglobulin heavy chains," Proceedings of the National Academy of Sciences of the United States of America 1979, 76, 7:3416-9; J. Martinis and C.M. Croce, "Somatic cell hybrids producing antibodies specific for the tumor antigen of simian virus 40," Proceedings of the National Academy of Sciences of the United States of America 1978, 75, 5:2320-3; H. Koprowski, W. Gerhard, T. Wiktor, J. Martinis, M. Shander, and C.M. Croce, "Anti-viral and anti-tumor antibodies produced by somatic cell hybrids," Current Topics in Microbiology and Immunology 1978, 81:8-19.

Southern California, but she eventually flew out to San Diego to take a look, and signed on soon after. "I think she saw," says Royston, "that we knew what we were talking about, and realized the potential was there."

Gary David continued to work with new antigens and antibodies while organizing the company's immunochemistry section, but with the arrivals of Curry and then Martinis, Howard Birndorf's career as a laboratory technician came to an end. He became occupied on a full-time basis with the duties of the chief operating officer. At first, those duties consisted mainly in paying the bills, hiring people, building out labs, obtaining equipment and supplies, securing antigens and cell lines, changing light bulbs, and generally making sure the staff scientists had everything they needed. There were no manufacturing or marketing functions to take care of because there were no products, but that would soon change. Royston's days as a contributor at the bench were numbered, too. In the beginning, he was visiting the company regularly, usually late in the afternoon, to do his consulting. Mostly, he looked at cell cultures and tended to cell lines: "I would get calls, you know, 'Can you come over and look at these cells?' And I'd say, 'Yeah, they look good,' or whatever. I was sort of a doctor to the cells." It wasn't long, though, before the labs established their own routines and rhythms, and the scientists and technicians began occasionally to express irritation at what they considered an outsider's intrusions. "Ivor came over periodically," says one of them, "and went through the lab and harassed everybody." Ted Greene, who would replace Brook Byers as president of the company in March, recalls: "By the end of 1979, or thereabouts, finally one of the scientists came to me and said, 'If you let Ivor into the lab again, I'll quit.'"

Royston remained involved in upper level management discussions from his seat on the board of directors, and in broad scientific strategy deliberations as the first member of Hybritech's scientific advisory board. He also continued to interview all applicants for open positions in the company, and he participated in weekly technical planning meetings held in the lab on Friday mornings. In the beginning, the company was small enough that everybody participated. Royston would bring doughnuts, and record and distribute the minutes. But, as the company grew, his direct involvement in the scientific end of the operation declined, and finally evaporated altogether. Royston was concerned with getting monoclonal antibodies into the clinic, in order to test them as cancer therapies. He wasn't very interested in learning about the antigens that the company was planning to investigate as possible targets for diagnostic tests. He was busy at the La Jolla VA Hospital and the UCSD Cancer Center making antibodies to human T and B cells, and employing them as instruments to map cell surface antigens, and particularly those molecules that could be used to identify and distinguish leukemias and lymphomas.[4] Royston's interest in monoclonal antibodies derived from their potential as tools for treating or curing cancer by immunological means. Hybritech intended to get into that business eventually, but Royston didn't want to wait.

---

[4] I. Royston, J.A. Majda, S.M. Baird, B.L. Meserve, and J.C. Griffiths, "Human T cell antigens defined by monoclonal antibodies. The 65,000 dalton antigen of T cells (T65) is also found on chronic lymphocytic leukemia cells bearing surface immunoglobulin," Journal of Immunology 125: 725-731, 1980; I. Royston, J.A. Majda, G.Y. Yamamoto, and S.M. Baird, "Monoclonal antibody specific for normal and neoplastic human T cells," pp. 537-540 in Protides of the Biological Fluids, Proceedings of the 28th Colloquium, H. Peeters, ed., Pergamon Press: Oxford, 1980; R. Taetle and I. Royston, "Human T cell antigens defined by monoclonal antibodies. Absence of T65 on committed myeloid and erythroid progenitors," Blood 56: 943-946, 1980.

After developing the first hepatitis antibodies – which Hybritech planned to market as research products in order to generate its first revenues – David and the other scientists who had come on board started to think about other antigens, other biological targets against which they might direct monoclonal antibodies. These were chosen principally on the basis of anticipated market demand and clinical usefulness, and secondly, on feasibility – some antigens posed greater technical challenges than others. For example, Royston had selected hepatitis for the proof of principle experiments because all blood supplies had to be screened for hepatitis infection. Before the identification of HIV as the cause of AIDS, demand for no other diagnostic test was greater. Blood banks, hospitals, and clinical laboratories all screened for the virus. Technically, however, hepatitis was difficult. It had proven to be an excellent immunogen. The virus elicited powerful humoral immune responses in immunized mice, and when splenocytes taken from these animals were fused with myelomas, the researchers discovered that the procedure had produced many different monoclonal antibody-producing clones from which they could choose. However, the very quality of the virus that made it a good immunogen, namely, its complexity and antigenic polymorphism, made it a poor candidate for diagnostic detection by monoclonals.

Monoclonal antibodies home in on molecules with laser-like precision. This is what makes them superior to polyclonal mixtures in many applications. However, if the target isn't precise and constant, then antigen-antibody interactions in immunoassays won't be, either. The variability of antigenic determinants among different subtype populations of the hepatitis virus introduced the problem of overspecificity. The Hybritech researchers found it difficult to calculate reliable data

on affinity constants for the antibodies they had developed. When tested against a battery of viral particles derived from different sources, the antibodies performed inconsistently – they gave different quantitative indications of analyte concentrations across samples and exhibited different levels of cross-reactivity.[5] Reliability depended on the identification of a precise antigenic determinant common to the entire range of viral subtypes, and a viable product would depend on the identification of an antibody exhibiting sufficient affinity for that determinant, as well as properties that would enable it to perform under the conditions of the test. Given the complexity of the virus, and the fact that viruses depend on antigenic modulation (the ability to change their coats) as a survival mechanism, finding that specific antigen and that specific antibody could require a good deal of time, energy, and money. Hybritech still planned to produce a diagnostic test for hepatitis B, but only because the market for a monoclonal-based assay promised to be massive. The development costs of the product could be high. The company scientists advocated some caution:

> [O]ne might speculate that the application of monoclonal antibody technology to immunodiagnosis will result in major advantages over polyclonal antisera in certain antigen systems such as normal serum components, but may run into some difficulty when other systems (such as viruses) are considered.[6]

So, the researchers were learning about the strengths and weaknesses of monoclonals and their experimental system. They were accumulating knowledge that

---

[5] G.S. David, W. Present, J. Martinis, R. Wang, R. Batholomew, W. Desmond, and E.D. Sevier, "Monoclonal antibodies in the detection of hepatitis infection," Medical Laboratory Sciences 38: 341-348, 1981.

[6] G.S. David, et al., "Monoclonal antibodies in the detection of hepatitis infection," Medical Laboratory Sciences 38: 341-348, 1981.

enabled them to make better, more informed strategic decisions. Among other antigens given strong consideration for development was CEA. Like hepatitis, CEA featured a great deal of allotypic variance, but the company elected to investigate the molecule anyway because Gary David was so familiar with it. The existing demand for colon cancer immunodiagnostics was high, but clinicians were roundly dissatisfied with results obtained from available tests. The company guessed that the large market would certainly expand immediately following the invention of a monoclonal-based assay. The Hybritech team also began working with PAP (prostatic acid phosphatase), an enzyme that serves as a blood serum marker for advanced prostate cancer, especially if the cancer has spread to bone. Before tests for prostate specific antigen (PSA) were developed and marketed (Hybritech was the first company to do it, in 1986), measuring serum levels of PAP was the most common non-invasive method of distinguishing prostate cancer from benign prostatic hyperplasia, i.e., non-malignant enlargement. CK-MB, an isoenzyme of creatine kinase, was also selected for special attention. CK-MB is associated with damage to the heart muscle; it is an indicator of heart attack. The company assumed that an improved CK-MB diagnostic would certainly become a valuable commodity. Finally, Hybritech licensed one of Royston's T-cell antibodies, called T101, from the University of California, and assigned it to a fast development track. The company intended to manufacture quantities for use by clinicians. It also planned to use the antibody to begin investigating cancer diagnostics and therapeutics.

A number of hormones were included among targets that were investigated early on, but were initially assigned a lower priority status. These included thyroxine

(T4), which is measured to diagnose thyroid disorders, and human chorionic gonadatropin (HCG) and luteinizing hormone (LH), elevated serum levels of which identify pregnancy and infertility, respectively. Experiments were also conducted with alpha fetoprotein (AFP), a substance produced by fetal livers. The presence of AFP is a marker of certain cancers, and in the blood of pregnant women can signal Down syndrome and neural tube defects. In order to diversify its R&D capabilities, the company aimed to develop expertise in working with small molecules, as well. It examined a few members of the aminoglycocide family of antibiotics, including tobrymicin, gentamicin, and amikacin. And, again for the purposes of broadening the group's experience and skills, and expanding its repertoire of tricks, Hybritech researchers developed some second antibodies (anti-antibody immunoglobulins) including Rh factor anti-D, IgG molecules that neutralize antibodies directed against Rh antigens on red blood cells, and anti-IgE, antibodies that detect the class of immunoglobulin involved in allergic reactions. Although work with IgE was originally considered a sideline project, a test kit for the molecule would later become the company's first diagnostic product.

ORGANIZATIONAL INNOVATION

Through October 1979, the company's first anniversary, the Hybritech research team was occupied with investigating various antigens, screening clones, assembling libraries of antibodies, and refining, streamlining, and scaling up all of their procedures and processes. As the company scientists moved forward, they were breaking new scientific and technological ground. They were also breaking new organizational ground. Hybritech was an unusual commercial enterprise because it

housed cell biologists, people who were not, at that time, ordinarily found in industrial settings, and because it employed methods devised in academic biology labs. These techniques were foreign to the paradigms – the sets of practices – that characterized research and development in the diagnostics and pharmaceutical industries. In the 1970s, academic bioscientists had their own conventions and customs. This is still true in many respects, of course, but the invention and commercialization of biotechnologies has, in recent decades, dramatically altered the relationship between academic biological research and industrial biological research. In the 1970s, the two spheres were far more distinct, in both technical and institutional terms. In any event, many academic conventions and customs were incorporated into the Hybritech way of life. Work routines in the labs at Hybritech were not very different from the work routines found in the labs of universities and non-profit research institutes.

The company displayed some family resemblances to other biotech firms that been previously established – Genentech, for one, up in South San Francisco. Genentech was likewise a science-driven operation, populated almost exclusively by young academics, and the unconstrained collegial environment fostered within it was similar in many ways to the atmosphere that emerged at Hybritech in its early days. Journalist Penni Crabtree reports that:

> Hybritech earned a reputation for both working hard and playing hard. Most of the management and scientists were in their late 20s to mid-30s, which created a charged youthful corporate culture. Every Friday afternoon at 4:30, beer and wine flowed freely at Hybritech, and scientists would chat with their bosses about research projects.[7]

[7] Penni Crabtree, "A Magical Place: Hybritech Launched San Diego's Biotech Industry," San Diego Union-Tribune, September 14, 2003, p. H-1.

The description could fit Genentech just as well. The same kinds of activities were regularly reported there, and the firm encouraged the same kind of informal approach to the conduct of research. Brook Byers had been involved in the formation of both companies, and he was shuttling back and forth regularly between the Bay Area and San Diego in order to observe, advise, and help out at Hybritech in various ways. It would be reasonable to suspect some kind of organizational mimesis at work. Gary David discounts the idea. Certain elements of the Hybritech operation, like offering stock to employees as compensation and TGIF rituals (at Genentech they were called 'Ho Hos'), may have been borrowed, but David insists that the company followed its own developmental path. In his recollection, Byers' influence in the labs was limited, mostly, to the imposition of fiscal discipline:

> There certainly was a level of driving by Kleiner-Perkins, mostly Brook, mostly Byers, because he was the one that was there, although Perkins was involved as well. And they certainly helped us keep on track, and made sure we didn't lose track of the financial projections, but the company, the research side, the R&D side, which was what most of the company was in those days, I think pretty much evolved, which is a nice way of doing things. I think even today, it's a nice way of doing things. Every new company is a new entity, and really should look at some models, but it shouldn't necessarily try to follow someone else's model.

The scientists and technicians who signed on to work at Hybritech and helped to organize the company's R&D program were moving into uncharted territory. They didn't have maps or models to which they could refer along the way. As Russ Curry says: "Things in the biotech industry were very different then, as in 'What biotech industry?'" In a sense, the biotech industry didn't come into being until October 14, 1980, the date of Genentech's initial public offering of stock. Prior to that, Genentech

hadn't made a big impression on the public. In the summer of 1978, Genentech researchers announced, with collaborators at City of Hope National Medical Center, that they had synthesized the gene for human insulin. That caught the attention of life scientists. But in early 1979, as Hybritech was getting underway, Genentech was still just a laboratory. It wasn't the subject of much discussion in San Diego or anywhere else. Lots of Genentech employees were holding company stock, but nobody had gotten rich. The Friday afternoon beer bashes weren't yet the stuff of biotech legend. Nobody was talking about 'biotech culture.'

Before October 1980, new life science start-ups had to establish their own practices without role models. This clearly changed later, once extensive networks of communication and exchange had been established within the field, but structural isomorphism and cultural likenesses among organizations in the early days of the biotechnology industry resulted mainly from parallel transfers of academic practices to new commercial entities. In the earliest stages of the industry's development, similarities probably did not often result from contacts between distantly located start-ups, or the diffusion of practices from one company to another. The financial practice of offering stock options as compensation was clearly an exception. This was a Silicon Valley high-tech start-up tradition that venture capitalists continued when they began funding and directing new biotech firms. Because it was foreign to academic institutions, considering how the practice was perceived at Hybritech tells a lot about the attitudes and motives of the scientists within the organization, and the kind of culture that characterized the place. Kleiner, Perkins, Caufield, and Byers were convinced that distributing equity was important for building employee loyalty and

company morale, and Royston and Birndorf had proposed it in their business plan. So, all of Hybritech's early employees were offered company stock at very low prices when they joined, along with options for later purchases. Gary David suggests that the securities were appreciated, especially after the Genentech IPO, and that they served their organizational purpose:

> This was at a time when Genentech, and maybe Cetus, were going gangbusters, and people were becoming rich. Janitors – this was the lore – were becoming rich because of their stock. And since everybody really believed we would be a hot company at some point, I think that helped make sure that the stock was very meaningful to people. Plus, the gesture – 'You're an owner' – means a lot.[8]

Other early recruits indicate, though, that the shares and options were not so important, especially before Genentech made its many paper millionaires. Russ Curry concedes that he didn't fully appreciate the commercial potential of monoclonal antibodies: "I didn't tumble to the business importance of them." He didn't expect any extraordinary windfalls. Joanne Martinis says: "When I came to Hybritech, I did it on a lark. I never expected the stock to be worth anything."[9] Jeanne Dunham, who arrived in January 1980 to set up Hybritech's first manufacturing operation says: "It didn't mean all that much. To me, the salary was more important at that point in time, because I had two young children." When asked what convinced him to leap from UCSD to industry, Walt Desmond answers: "It wasn't financial." Greg Payne remembers being a new graduate of UCSD who was "just glad to have a job. I just

---

[8] Times have changed, and so has the status of janitors at Genentech. See Associated Press, "Genentech OKs Paying Janitor Health Costs," May 10, 2003. The AP reported that "Biotechnology giant Genentech Inc. volunteered Friday to chip in for the health insurance costs of janitors who clean its headquarters, an unusual move that may pressure other corporations that rely on outsourced maintenance crews to do the same."

wanted to have a job." Bruce Birch was the carpenter who built three laboratories for Hybritech at the La Jolla Cancer Research Foundation. After some tense haggling over the price, Birndorf showed up while Birch was working, with a peace offering, a twelve-pack of beer. The two got to know each other a bit. After the labs were constructed, Birndorf offered Birch a job as the firm's first maintenance engineer. He was handed badge #27. Then, according to a story appearing eight years later in a company newsletter:

> Howard came to Bruce bearing stock options and was met with some resistance. "Don't give me that worthless piece of paper, I want a decent salary," Bruce demanded. Howard insisted that the options might someday be worth something, but Bruce wasn't impressed. He admits later that he felt like a fool, albeit a happy one as he cashed in his penny stocks.[10]

Cole Owen, later a manager of various departments at Hybritech, points to the firm's demographics as an explanation for the lack of enthusiasm regarding the stock options: "You have to keep in mind that the average age in the company was twenty-eight, I think, for a long time. Twenty-eight year old people don't care so much about retirement issues." Certainly, when Hybritech went public and the shares acquired some actual value, they also became more meaningful to many. Nevertheless, even years later, the scientists still often displayed indifference toward the equity they were offered. Tim Wollaeger, who became Hybritech's chief financial officer in 1983, describes the attitude he discovered among many researchers:

> I remember having a discussion once with a high-level person we brought in. I offered him some stock options, and he said to me, 'Oh, you financial guys, you think you're going to give me these stock

---

[9] Grant Fjermedal, Magic Bullets, p. 128.

[10] Pat Woods, "And Our Maintenance Guru Tells a Tale," The Magic Bulletin, December 1987, II, 7: 5.

> options and make me happy. If you really want to make me happy, what I'd rather have you do is give a microscope to UCSD in my name. I said, 'If you'll give me your stock options, I'll buy the microscope.' I could have done that, but you have to sit there and say to them, you know, 'This is real money. If things work out, this could mean a lot to you, you've got to see some value in that.' Now whether they did or not, I don't know. Probably when it became real and they could buy stuff, it did.

Many of the people who were at Hybritech in the late 1970s and early 1980s describe it as a special place. It wasn't the salaries that made it so – these were just on a par with university wages – and apparently, it wasn't the securities or opportunities for accumulating personal wealth, either. Hybritech was special, and unique, because of the kinds of people who were there and the kinds of things they were doing together. Why had these scientists decided to leave academia in order to join an unproven and uncertain start-up venture? The move wasn't considered a particularly deft one at the time – colleagues and friends of jumpers typically questioned it and cautioned against it. Russ Curry remembers being warned that "if I crossed the street from Scripps Clinic [to Hybritech], my career was over." Walt Desmond was aware of the possible ramifications, too: "It was considered risky just to leave academia. In biology, it's quite a bit different now, but at that time it was irreversible." Joanne Martinis reports that when she announced her intention to join Hybritech, the little start-up in Southern California, "Everyone told me I was a fool."[11] Since biotechnologies have become so well-established, and since large corporations in the diagnostic and pharmaceutical industries have uniformly begun to adopt state-of-the-art biological and biochemical methods, there is today more far more interplay

[11] Grant Fjermedal, Magic Bullets, p. 128.

between academia and industry in the life sciences, and far less distinction. In those days, however, the institutional boundary separating the two was rigorously policed. Why did people start crossing it?

For some individuals, chances to get rich were probably sufficient incentives to move them to abandon traditional academic careers. After venture capital investments and splashy Wall Street goings-on had become familiar news items around universities and the biomedical industry, and some senior academic investigators had begun getting involved in entrepreneurial ventures, scientists and technicians adopted new attitudes about moving into industry. Their perceptions of risk were transformed. Bob Wang, Gary David's colleague from Scripps who rejoined his friend at Hybritech to work on product development, remembers hearing a new kind of opportunistic talk in the scientific community: "'Hey, it's a slam dunk. I'm going to join a start-up and become very rich.'" That expectation has become increasingly unrealistic. Venture capitalists have become far more tight-fisted with equity shares, but the notion persists. "It's amazing, that mentality is still there today, to some extent," says Wang. "People think that they're going to join a start-up company, and more likely than not become very wealthy." For a few entrepreneurial scientists – those in charge of labs that make important and potentially valuable scientific discoveries – there are still opportunities to generate significant personal wealth by founding venture capital-backed biotech companies. Today, after more than twenty-five years in the business, Howard Birndorf has a lot to say about scientists who commercialize their research. He has observed that, for some, making money is a very important motivation:

> Some of them are the greediest sons of bitches you ever saw. They think their ideas are worth the world. One came into my office and pounded his fist, and said, 'Don't ever think that I'm not interested in money' – even though his whole façade was the old scientist driving the old VW bug, he was a greedy son of a bitch. And of course, he'll probably say the same thing about me. He thinks I tried to screw him out of fifty thousand dollars once, so he has this big thing about it.

Birndorf has also observed, however, that "Some scientists are in it just to get their ideas put into practice, you know? They don't really care about the money. They really just don't care about it." And those without technologies to hawk may be drawn to scientific challenges in the same way. According to Birndorf, "if you have a leadership position with your technology, you can attract the best scientists. They're not just motivated by high salaries but by the opportunity to work in the forefront of a technology."[12] Tim Wollaeger believes that despite real chances for life-altering financial gains during the biotech boom of the early 1980s, the exodus of biologists, biochemists, immunologists, and medical researchers from academia to small entrepreneurial start-ups during this period took place mainly for reasons other than money. Even after stories about new biotech millionaires had become commonplace, he says:

> People left the university to come to Hybritech because they thought that the labs were better, and they could have greater freedom in terms of what they were doing. They didn't have to write as many papers. They didn't have to worry about applying for grants. All they had to do was science.

At Hybritech, the technical aspects of scientific work were paramount, and that was attractive to young researchers. The company spoke a language that recruits understood. Gary David's sales pitch to prospective scientists and technicians

emphasized that Hybritech was experimenting with an "exciting new technology" and that working at the firm was "a lot of fun."

THE NEW REPUBLIC

Hybritech was a science-driven company. The scientists and technicians showed up to work there because the firm was a place for them to participate in challenging, engaging projects. They recognized that the nature and conditions of industrial research had changed. The scientific goals were basically the same as in academic laboratories, but the institutional context was different. The rules of the game were different. For instance, the new republic of science founded in young biotech start-ups was to be a meritocracy. Ideally, decisions regarding rewards, promotions, and assignments were to be based, not on credentials, bureaucratic conformity, or obligations imposed by the medieval system of patronage found in universities, but rather on ability and technical accomplishments. The environment was perceived by those in the vicinity to be freewheeling and wide open. At Hybritech, there were opportunities for young scientists and technicians to move up in the organization, and some took advantage of them.

Gary David was the third person hired by the company. Employee #4 was a young man named Billy Present. Present was hired as a cage washer in the animal room. "It became obvious pretty quickly," says David, "that Billy was very bright and could do good work, so he ended up moving into the lab and he ended up being one of our primary technicians." Company legend eventually included a number of stories about lab technicians who, due to their own initiative and accomplishments, ascended

---

[12] Gerald Parkinson, "How to Succeed in BioBusiness," Chemical Week, December 9, 1987, pp. 46, 50.

the company's chain of command to direct their own groups. Greg Payne came into the company early on with bachelor's degree, but was promoted through the ranks to become a staff scientist and manager in the firm:

> I had planned on working for a couple of years, and then going back to school, but I just got caught up in everything here at Hybritech, and there were always lots of opportunities. And one of the things that's nice about working in industry as opposed to academics is there wasn't the same stigma attached if you didn't have a Ph.D. In academics, you're not going to go anywhere without a Ph.D. But in industry, if you worked hard and had proven abilities, you get to the same level.[13]

When Payne came on, the company was paying lab techs $12,000 per year. "I got hired in pretty inexpensively," he says. "I settled for the low wages because if you don't have experience, you have to get it somehow." Once on the inside accruing the experience he sought, he began to identify possible career paths to follow. He acquired a sense of the reasonable possibilities for upward mobility in the firm. Satisfied with what he found, he made a commitment to stick with the organization, to do what was required in order to get where he wanted to go: "I wanted to get to the research scientist level in assay development, that was my goal." Payne did good work and began moving up. "After several years, I was probably the person in the lab," he says. "I had a lot of people reporting to me on a daily work basis, including a bunch of part-time people. So, the amount of autonomy I had increased over time as my skills increased." He eventually surpassed his original objective. After a time, he was handed a ticket out of the laboratory and into management. "As you move up the ranks, you work in the lab and you're good at what you do, you're good at working at

[13] Payne adds that, at Hybritech, and in the biotech sector generally, non-Ph.D. holders still reached promotional plateaus earlier than Ph.D.s in the upper echelons of organizations.

the bench, so they promote you to work as a supervisor, and you're out." In universities, principal investigators are also required leave the bench behind, for the most part, when assigned their own laboratories to direct. They become administrators. Some are pleased by the change, others are not, but in universities, a Ph.D. is required to make the transition. The same isn't necessarily true in commercial biotechology, or it wasn't, at least, in the formative stages of the industry.[14] The rules of the game were different.

In 1979, Hybritech was a pure research operation housed within a commercial enterprise rather than an academic institution. In the beginning, at least, the company's scientists wanted just to perform good, careful experiments in order to expand bodies of scientific knowledge, just as they would have (in theory, at any rate) in any university laboratory. They refused to distinguish what they were doing from basic inquiry. Aware of this way of thinking among industrial biotechnologists, Ray Kahn, former director of technology transfer at Scripps, has commented, "You can

[14] Promotions and raises were not the only ends pursued by Hybritech employees. Some found other reasons to work the long hours that start-ups typically require. Marty King, for example, was a lab tech who joined the company in 1978. When he first arrived, he says, "There was nothing there. Just ideas. We were starting from the beginning." As demanding as it was, King enjoyed the work immensely, and he witnessed the operation mature "from nothing to a product on the market." He found himself gradually transformed by the experience. He was impressed by the science, but also by the good that he imagined could be done with it. He had arrived at Hybritech with a bachelor's degree in chemistry, just looking to make a living, but he eventually became deeply committed to biomedical research. "At first it was just a job, something I knew I could do. But the more I understood what Hybritech was trying to do, and the more I got to know Ivor Royston, the more respect I got for the industry, and the more excited I got." When he left Hybritech after seven and half years, it was to take a job as a lab manager at a second company started by Royston in San Diego, called Idec. Idec was founded to develop monoclonal antibody-based therapies for lymphoma. "To find a cure, a vaccine, that's the ultimate. What more could you want, but for your company to come up with it, and for you to work for that company – no matter what you do. It's your life work, and it can become an obsession." See Tom Gorman, "The Faces Behind Biotech: The Technicians," Los Angeles Times, May 30, 1991.

insult these people by saying they do applied research."[15] Daily actitivies at the bench were much the same as in an academic setting, but, in order to sustain projects at Hybritech, David explains, "We didn't have to write grant proposals – although we did, anyway. Our futures weren't dependent on getting grants from the government." Hybritech and a few other biotech start-ups were working out a new way of supporting scientific work. As scientific entrepreneurs and venture capitalists began transforming the institutional landscape by founding and funding small biotechnology companies, scientists and technicians began adapting to the changes by creating new kinds of scientific communities within these organizations.

Gary David played an influential role in defining the new scientific culture at Hybritech. He was the first scientist on the scene at the firm, and he set the tone for others in the company's labs. He was quiet, but he commanded respect. He was highly regarded for his expertise in immunodiagnostics, certainly, but perhaps even more for his equanimity. His co-workers appreciated his authenticity and charity. Like his mentor at Illinois, Al Nisonoff, he displayed an enthusiasm for scientific work, and like Charlie Todd, his former boss at City of Hope, he was open, encouraging, and fair as a lab director. He engendered confidence and loyalty among the company's scientific staff, and was enormously influential in the early days of the company. In 1983, science writer Grant Fjermedal visited Hybritech and observed that:

> Dr. David seems to be viewed by many of the scientists as their spiritual guru and protecting saint. For instance, one story is that, early on, a new scientist was hired and showed up for work on the first day

[15] Tom Gorman, "S.D.'s Biotech Industry Is Rooted in Academia," Los Angeles Times, May 27, 1991: A-1.

> wearing a necktie. On the second day the tie wearer was joined by one of the existing employees, who figured that if this new guy wore a tie then he better, too. On the third day there were three scientists in neckties. On the fourth day, Dr. David joined them. He had a busy schedule that day, including meetings with president Ted Greene and a visit from an investment banker. Throughout the day he wore his necktie without comment, as if nothing could be more natural. The rest of his wardrobe consisted of old tennis shoes, jeans, and a T-shirt. The guru had spoken.[16]

For David, always, the science came first, and after his unpleasant experiences at the Salk and Scripps, he believed that it was best pursued free from administrative interference and insulated from political squabbling. At Hybritech, he was the chief scientist from the beginning, and he was able to persuade the work crews he ran to adopt his own personal standards for both excellence and informality in the conduct of research. He tried to create at Hybritech the kind of atmosphere that he had hoped to find in academic institutions, but had not. David had concluded that the academic way of keeping score, distributing rewards, and allocating resources was antithetical to the growth of scientific knowledge. His experience in organizing cohesive scientific teams and overcoming many difficult technical challenges in order to make Hybritech a success only confirmed his thinking on the subject. The competitive 'publish or perish' rules of academic science, David came to believe, more often inhibit rather than promote the kinds of communication and cooperation that are necessary for scientific progress. And because the academic reward system provides incentives for the production of quantity at the expense of quality in scientific work, standards of rigor have gradually become degraded in academic science, and creativity and innovation are commonly discouraged and penalized:

---

[16] Fjermedal, Magic Bullets, p. 125.

> Most [scientists] out there will admit to this. In order to ensure their futures, they are forced to publish things that are based on less than complete information, less than complete experience. They are forced to do a lot of experiments fast, get a lot of data, write it up in as many ways as possible, and put out a volume of publications. Or else they aren't going to get their next grant.[17]

While defending the value of academic freedom, and acknowledging that, historically, most important – and useful – discoveries have emerged from basic rather than applied or directed research, David suggests that "the system has forced a lot of potentially very good people into doing mediocre work."[18] After his experience at Hybritech, he came to the seemingly paradoxical conclusion that 'pure' science is probably more often pursued in industrial laboratories, or, at least, in the laboratories of small, fledging start-up companies, than it is in universities or non-profit research institutions. Bob Wang describes how it was at Hybritech: "There was a good atmosphere to present your ideas, technical ideas, and be challenged, and be able to deal with the challenges and differences in constructive fashions. There was a real sense of camaraderie and teamwork at the time." This is what Gary David was after. He was at Hybritech because he perceived it as an opportunity to do interesting scientific work in a conducive environment, without the burdens of teaching and administrative duties, and without publishing and fund-raising pressures. He believes that many of his co-workers jumped to the start-up from UCSD, Scripps, and Salk for the same reasons:

> I suspect that a lot of people at the time were also starting to develop the attitude that I had developed a couple of years before that, that academic science wasn't what we thought it would be. You didn't have

[17] Fjermedal, Magic Bullets, p. 196.

[18] Fjermedal, Magic Bullets, p. 196.

> the freedom to do the kind of research that you wanted, and it was getting harder to get grants, and certainly there was a lot of administrative shit to put up with.

The special quality, the appeal, the 'charisma,' that the Hybritech people perceived in their company had much to do with the unique technical tasks that the firm had staked out as its own, and the unique ways in which the members of the organization, collectively, went about accomplishing them. The company offered scientific challenges – difficult technical problems with many unknowns and uncertainties. People working with monoclonal antibodies in 1979 were pushing at the limits of knowledge in the life sciences. That meant a great deal to the young scientists and technicians at Hybritech. They wanted to learn things, and make things happen, and they wanted to be recognized for it. They wanted to be good. They enjoyed being on the cutting edge. They took pride in it. Greg Payne says: "I was pretty impressed with the technology and the fact that we were one of the leading companies in the exploitation of monoclonal antibodies." Walt Desmond admits that he didn't really understand what he was getting into at Hybritech, but he acknowledges that the attractive element was the science: "I have to say that I didn't know anything about manufacturing, and it was sort of faith that there were actual business and medical applications. I guess I was more interested in the science. I guess it was a challenge." In the early days, there was a spirit of optimism in the company's labs. Hybritech's scientific group was out to prove the technology and prove themselves to those expressing doubts about the value of monoclonal antibodies. They thought of themselves, in a sense, as revolutionaries challenging the

established order of things. On the reticence, initially, of many others to embrace hybridoma technology, Gary David says:

> There certainly was skepticism, as there is with any new technology. Science is unfortunately a conservative community, and scientists, especially when you get into medical circles, are very slow to change, but I had no doubt that it would be, nor did my colleagues there, have any doubt that it would be a commercially viable. I was not skeptical. I knew it would have great commercial uses. I don't think I realized the extent to which it would take over the community, or the speed with which it would take over the community, but I was convinced from the beginning.

It was a heady time; the cliché is apropos. The Hybritech opportunity generated a lot of enthusiasm among the young researchers. It felt good to be loping ahead of the pack. Desmond says, "The atmosphere was very exciting." David says, "We were on a roll. When people came to interview, we could tell them about the work we were doing, and it was exciting. We were learning new things. We were breaking ground. And that's the sort of thing that should, and usually does, turn on scientists." The excitement, in turn, elicited strong commitments from the individual members of the team. Desmond says, "Everybody was working hard, and I remember very well, people routinely came in Saturdays." Gary David set the example and the pace. As Payne recalls, "It seemed like Gary was always there." According to David, "Those were probably twelve hour days on average. Going back at night was automatic, and I remember many all-nighters. That was the way of life." David was pleased with the scientific progress that the firm made early on, and pleased as well with the organizational culture that had been created in the labs: "We were a bunch of scientists, and we were a bunch of scientists out of academia, so, as you would expect, there were occasional friction points. It had its ups and downs, but we managed to

make it through. It worked pretty well." Howard Birndorf concurs, in rosier shaded tones: "It was an amazing thing, a well-oiled machine where people worked well and were happy. Those first years were really remarkable – it was a magical place."[19]

For the Ph.D.s and the technicians, the science was a big part of the 'magic.' The technical 'sweetness' of the company's projects, the promise of monoclonal antibodies in practical application, and the collaborative process of bringing the technology to fruition within the firm's unique cultural and organizational setting made a combination that was difficult to resist. Many of the scientific people at Hybritech had become captivated, and some perhaps obsessed, by antibodies in their scientific training. Walt Desmond expresses awe when talking about the properties of immunoglobulins and their functions: "antibodies are just amazing things, you know. It really is an incredible mechanism." The humoral immune response, the production of antibodies, is an organism's early warning and defense system against invading pathogens, foreign tissues, and toxins. Nature has programmed it to generate proteins that recognize and defend against an almost limitless number of antigens. Nature has also created plenty of work for immunologists – the immune system is awe-inspiring in its complexity.

In vertebrates, diversity in the repertoire of antibody specificities owes to deletions of DNA and the rearrangement of antibody genes in the processes that differentiate B-lymphocytes. Every lymphocyte (or, in the Hybritech case, every hybridoma cell line) produces a different antibody, a unique protein defined by the

---

[19] Penni Crabtree, "A Magical Place: Hybritech Launched San Diego's Biotech Industry," San Diego Union-Tribune, September 14, 2003, p. H-1.

expression of different light and heavy peptide chains in the variable region of the molecule. The phenotypic permutations that can result from these random deletions and recombinations number in the millions. The immune system is thus able to produce millions of different antibodies that will react with millions of different antigenic determinants. For some investigators, these facts, as formulated by the disciplines of molecular immunology, cell biology, and genetics, describe a phenomenon of astounding beauty and a source of lifelong fascination. Gaining some control over this biological process was unexpected, and many laboratories redirected their paths of research when it occurred. The Hybritech group was among the first, and for many of the individuals involved, it probably seemed like the chance of a lifetime (and maybe it was).

Hybridoma technology permitted bioresearchers to isolate and maintain supplies of hybrid clones that secrete immunoglobulins designed to target specific molecular binding sites on antigenic substances. When they learned of it, immunologists, biologists, and medical researchers everywhere were delighted by the invention of this tool that could conceivably solve so many problems for so many people. The arrival of the technology in San Diego was stimulating for local bioscientists. And the fact that the Hybritech group happened, partly by chance, and partly due to the efforts of Royston, Birndorf, and their financial partners, to be well ahead of their competitors on the learning curve, only added to the collective sense that they were part of something special and important. The Hybritech researchers began eagerly and aggressively exploring the possibilities of the technology. Desmond tells about it: "Once we got into this thing, we came up with lots of ideas

about technological things we could do in the lab. It was a lot of fun sitting around dreaming up potential applications once you had some idea about the power of these things." Toying with immunoglobulins, analyzing their characteristics, and observing and manipulating their behaviors were activities that many at the company found absorbing. And working together, collaboratively, to make the organization successful, and to use antibodies to perform tasks of value to science and medicine, made employment at the firm all the more enjoyable.

The 'charismatic' quality of hybridoma technology that appealed to the early participants in Hybritech's scientific activities, and elicited their faith and devotion, was later effectively communicated to others in a partially reconstituted form. This was crucial for the survival of the firm, and so became a strategic objective pursued with vigor by the company's management team. Venture capitalists in later financing rounds, investment bankers and stock brokers on Wall Street, and members of the investing public became convinced that monoclonal antibodies were possessed of a special juju that could be translated into revenues and profits. Once given the word and persuaded, they expected antibodies to perform marvelous feats, and perhaps even cure cancer. Millions of dollars eventually poured into the company because belief in the 'magic' of the technology had been cultivated so adroitly by Hybritech showmen. But, for the researchers, the charisma of Hybritech wasn't derived exclusively from the reputed efficacy of 'magic bullets,' and it certainly wasn't based on the wondrous but mysterious powers of a technology that they knew only from the testimony of others, some anonymous experts. It was also experiential. It was about the thrill of

participating in something innovative, and something that seemed momentous. This was a thrill that investors could only experience vicariously.

Unfortunately for Gary David, however, the organizational space that he and his team had created for the pursuit of unencumbered science at Hybritech would not be preserved. When David accepted Howard Birndorf's offer to join the firm and handle its immunochemistry work, Birndorf was pleased to have found someone so talented and dedicated. He discovered quickly, though, that David "was not commercially oriented at all. I mean, really." In the beginning, when the R&D program was concerned mainly with working out the fundamentals of antibody production and characterization, a strong commercial focus wasn't required. So long as the immunochemist and his cronies delivered the technical goods – and they did – it made sense to respect their autonomy and leave them to their own devices. But Hybritech was a commercial enterprise. At some point, the company would have to start selling products and taking in revenues, and there were pressures on the scientists to move in that direction post-haste. Almost as soon as it appeared, the 'specialness' of the organization that attracted the first researchers began slowly to dissipate and to follow the path that sociologist Max Weber believed all forms of charisma were destined to travel – "from a turbulently emotional life that knows no economic rationality to a slow death by suffocation under the weight of material interests."[20]

The qualities that made Hybritech an attractive place for the scientists didn't disappear in an instant, and perhaps never vanished completely, not even after the

[20] Max Weber, Economy and Society, Vol. 2, ed. Guenther Roth and Claus Wittich, Berkeley, CA: University of California Press, 1978; p. 1120.

company was taken over by the pharmaceutical giant Eli Lilly in 1986. But the focus on product development that Hybritech had to develop early on was a new and sobering experience for the academics. Making and characterizing antibodies was just the beginning of the product development process, and not an endpoint for the firm. Kleiner Perkins' involvement was premised on the idea that the company would move directly toward entry into the immunodiagnostics market. From their point of view, a business that simply manufactured and sold quantities of research antibodies would not have justified the initial investment, nor the venture capitalists' commitment to see the firm through to profitability as long as that goal appeared attainable. The group that Birndorf and David had assembled was impressive – it was scientifically skilled and accomplished – but it had no experience in making diagnostics products or organizing a manufacturing operation. Russ Curry admits: "We were all very naïve about a great many things." Walt Desmond also comments on the lack of commercial savvy within the group:

> All of the people were from academic labs, and you know, there wasn't any manufacturing timeline or anything. There was a kind of urgency of realizing this thing, just getting it going. It was a pretty amazing situation. There was no budget, no particular timeline. We certainly had products that we had in mind. I mean there were plans, five and ten year plans, things like that, but we didn't really sense that, you know, 'We have to have this by December or March,' or something.

Jeanne Dunham, Hybritech employee #43, was one of the few early recruits who came into the firm with industry experience. She had previously spent five years at Behring Diagnostics in New Jersey, and then at Calbiochem, a reagent and immunoassay developer located in San Diego, after it had been purchased by Behring. She was hired by Howard Birndorf to design and scale up a manufacturing process

once the company was ready, in late 1979, to begin marketing its first research product – the hepatitis antibody. At Hybritech, she says, "Everybody was younger. Everybody was innovative, but everyone was research oriented, I mean everyone." What she found when she arrived was unlike anything she had observed before, and the experience was a bit disorienting. Hybritech was being run like an academic lab: "I thought, 'How can they operate like this?" Many of the scientists and technicians, curious about what was to come, started asking similar questions. They anticipated some kind of transformation as their worked progressed and they began to develop a collection of high-quality, functional antibodies. They, too, recognized that, having made some antibodies to this antigen or that, they couldn't simply move on to the next interesting thing. Joanne Martinis says that when she signed on to work at Hybritech:

> I figured the company probably had a fifty-fifty chance of making it. I knew that I knew how to make antibodies. And I knew that I didn't know how to sell them. And I knew that I could have the best scientific ability in the world, but unless there's a marketing and management system to do something with those antibodies, it's going to be another gleam in somebody's eyes that never got anywhere.

Putting a marketing and management system into place, developing a manufacturing process, and staffing the company with qualified personnel (i.e., business people with experience in the diagnostics industry), were all high on Brook Byers' list of priorities for the firm. As acting president, he was intent on rapidly transforming the tiny research boutique into a bona fide industrial outfit that made money by shipping goods. His first order of business was to replace himself. He had been commuting regularly from San Francisco to San Diego during the first few months of the company's history in order to assist and mentor Birndorf. The venture

capitalist and the former lab tech worked together to tackle the never-ending stream of tasks and petty emergencies that had to be managed in order to keep the start-up moving forward on an even keel. The commute and the demands of the job were wearing on Byers, and his desire to locate a permanent chief executive with industry experience was heightened when, after missing the Monday morning flight on which he ordinarily traveled to San Diego, the plane crashed leaving no survivors.[21] To Byers' relief, chance intervened once more in the Hybritech story, and a suitable candidate was identified and then hired on March 1, 1979. That began the gradual transformation of Hybritech from a bunch of scientists with a laboratory but no products, and no sure idea about how to develop one, to a major innovator in the diagnostics industry.

THE REFORMED CONSULTANT

Howard E. 'Ted' Greene was born in Akron, Ohio, in 1943. His father was an executive with the tire maker, B.F. Goodrich. When Greene was in high school, Goodrich sold the synthetics fiber division run by his father to Celanese Corp., which relocated the business to North Carolina. The Greene family followed the business. Ted completed high school in the Tar Heel state, and then traveled up the coast to attend the University of Massachusetts at Amherst, as a physics and chemistry major. He wasn't a star student, but he maintained a B average, and appreciated the mental discipline demanded by his chosen fields. As a senior, however, he delved into quantum mechanics, and the experience convinced him to pursue an MBA after

[21] See John W. Wilson, The New Venturers: Inside the High Stakes World of Venture Capital, Reading, MA: Addison-Wesley, 1985, p. 82.

graduation: "Have you ever studied quantum mechanics? Well, you find yourself on a Sunday afternoon sitting under a tree doing mathematics that makes no sense whatsoever from an intuitive standpoint, and you suddenly realize, 'This isn't the way I'm going to spend the rest of my life.'" He was married by the time he left Amherst, but a trust fund enabled him to pursue the graduate degree. He was accepted at the Harvard Business School.

After receiving his MBA, Greene took a position with the high-powered management consulting firm, McKinsey & Company. He focused primarily on strategic analysis, and began using time-sharing computers to develop financial models of acquisition and growth strategies for firms. His clients were chief executives of large corporations in a number of different industries, including chemicals, computers, and medical products. A favorite client was the chairman of the board at Baxter-Travenol, a medical supply company headquartered in Chicago. Greene spent a lot of time at Baxter, working principally with the company's Hyland division located in Costa Mesa, Orange County, California. Hyland was in the biologics business. It sold blood fractions for therapeutic use and immunodiagnostics products that incorporated anti-serum. After seven years at McKinsey, Greene got tired of advising executives and decided that he wanted to do some actual hands on executing. "The chairman of Baxter," he says, "figured it out, and, within a week, I was on a plane headed for Costa Mesa to work at Hyland."

As a reformed consultant, Greene was responsible for devising and implementing profit improvement and asset reduction programs at Hyland and Baxter's American Instruments division. For a year and a half, he commuted between

Chicago, Orange County, and Maryland, where American Instruments was located. He reported to the divisional presidents and the president of Baxter. Then, in 1976, he moved out to California permanently to become director of planning at Hyland. He was there for two tumultuous years. The division was in deep trouble. Greene tried to revive the business in various innovative ways, but the methods he employed were not always appreciated. He ruffled some feathers, for example, when he attempted to upgrade the division's product line. He began working with a young chemist named Tom Adams who had just come to Hyland from DuPont. They talked about improving the company's controls for blood chemistry tests. Greene filled Adams in on the requirements from a marketing standpoint, and Adams suggested licensing a DuPont freeze-drying technology that had not previously been used to treat assay controls. They proceeded to develop a new product, but the project was never approved in Costa Mesa. Instead, Greene took it back to Chicago to show to the president of Baxter. The home office was impressed, and Hyland was instructed to manufacture the new controls, but not everyone in the division was thrilled about the unorthodox manner in which the instruction came about.

Things got worse when Hyland set about marketing the new product. Greene and Adams believed that it should be sold at a premium price, as the crème de la crème of controls. The marketing department, however, "a bunch of ex-salesmen," in Greene's words, decided to position it among the lowest margin commodities in the product class and to sell it at a discount. That required the division to manufacture and move high volumes quickly in order to cover the high costs of implementing the new technology. There were manufacturing problems and, according to Greene, the whole

project became a fiasco. "They fucked it all up," he says. The frustration and disgust that he expressed with the process and the outcome didn't make him any friends. In 1977, Greene took over Hyland's international marketing program. By his own account, international sales came to exceed U.S. sales under his direction, and the division's profitability increased, but he again made some unpopular moves. One involved another product development controversy. Hyland was selling an automated immunoassay reader. Greene thought its reagent handling system was sub par. He worked with the head of Hyland's European operation to design a replacement, and found a European company to manufacture it. The project was unauthorized and when news of it reached Costa Mesa, Greene's colleagues were, for a second time, nonplussed by his maverick ways. The new reagent system was eventually incorporated into Hyland instruments on a worldwide basis, but the technical success of the project didn't repair Greene's reputation within the division.

Looking back and taking a broad view of his tenure at Baxter, Greene now understands why his actions prompted strong reactions. Hyland, he explains, "was an outlier in Baxter. Baxter basically fills bottles of water and makes latex gloves and things like that. As the division wound down, they kept trying to move corporate people in when what it really needed was an entrepreneur to run it." Baxter was a huge corporation that did not customarily solve local problems in its empire by decentralizing and delegating executive functions. The typical corporate response was exactly the opposite – to reduce the autonomy of distant outposts like Hyland.[22]

[22] In a corporate history of Baxter, Thomas G. Cody tells of an episode that took place at Hyland in 1970, just a few years before Greene's arrival. Believing that Hyland was slow to adapt to the new developments that occurred in immunology during the 1960s, the corporate leadership at Baxter sent a

Greene resisted the imposition of corporate control. He displayed little regard for established relations of authority, chains of command, channels of communication, and modes of conducting organizational business: "I was scrambling around, and sort of using my contacts and position and what not. I wasn't going to play the game. The game was corporate politics, you know, how to put in the right budget, how to say the right things at meetings. I didn't do that. Some people loved it and some people hated it." Although Greene had friends in the highest places, opposition to his activities grew: "I was gradually making myself persona non grata within Baxter."

After a round of quarrels within the company concerning the European incident, it became clear to his superiors, if not to Greene himself, that although he was talented and creative, he didn't really fit into the corporate mold. In the summer of 1978, Baxter – characteristically – decided to move Hyland's divisional headquarters back to Chicago. "That," as Greene tells it, "was the final blow. They took the opportunity to tell me that they weren't going to move my job – you know, 'you need to go do something else.'" The dismissal was friendly. Greene was informed in July that his services would no longer be required, but he remained on the Baxter payroll until March 1, 1979, the day he joined Hybritech. He still returns periodically to Chicago, now as a conquering biotech hero, to attend Baxter reunions. At one of these gatherings, the former chairman who had hired him from McKinsey said, "The best thing we could ever do for Ted was to fire him." And although it was

---

team called the 'Chicago Seven' to clean house and replace the entire upper management roster of the division. The surprise move came to be known within the company as the 'Costa Mesa Saturday Night Massacre.' See Thomas G. Cody, Innovating for Health: The Story of Baxter International, Deerfield, IL: Baxter International, 1994.

hard for him to accept, Greene concedes that it was the right decision. Looking back, he describes getting fired as "a galvanizing moment." He was thirty-five years old, and he had to figure out what he wanted to do:

> You've got to change. I tend to have a lot of trouble quitting what I'm doing. You know, once I get my brain into something, I just want to see the darned thing through. I get emotionally attached to it, and, in fact, I was very attached to Baxter. I was devastated. You know, they didn't want me. On reflection, it's pretty clear why they didn't want me. From their standpoint, I had been absolutely trustworthy, I worked hard, I had done some great things for them, but it was just like oil and water. You couldn't run a company that, by then, probably had ten thousand, twenty thousand employees, with a loose cannon rolling around, because the vast majority of them are, you know, all highly structured, non-risk takers, and so forth and so on. So, they gave me a kick in the side of the head.

Greene began putting copies of his résumé in the mail and spreading the word through his network of contacts that he was looking for a new job, but then a number of things happened to send him on a voyage into the biotechnology industry. First, he attended a scientific conference in the fall of 1978 with Hyland's chief technical officer. One of the speakers was a biologist from Cal Tech named Bill Dryer, who was scheduled to discuss a fluorescent reagent system that he was using. But when Dryer rose to make his presentation, he addressed a different topic and conveyed some information that made an indelible impression on Greene: "He said, 'Ladies and gentlemen, I'm scheduled to talk about fluorescence, but before I do, I want to talk about a breakthrough of huge magnitude, and you'd better pay attention to it, it's called monoclonal antibodies.'" Greene had never heard of monoclonals before, nor had anyone else at Hyland, to his knowledge. His companion at the meeting, the

company's CTO, knew nothing about them, and didn't appear to be particularly interested, either. But Dryer's presentation set wheels turning in Greene's head.

Soon after, Greene had a conversation with one of Hyland's scientists, who, like many in the division, was weighing whether he really wanted to move from Costa Mesa to Chicago. He was casting about for opportunities that would keep him in Southern California. Greene brought up the topic of monoclonal antibodies, and the scientist mentioned that he knew a cellular immunologist from New Zealand, named Jim Watson (not that Jim Watson, this was another Jim Watson), who was a member of the faculty at the nearby University of California at Irvine. Watson had gotten hold of some myelomas and was tinkering with hybridoma technology. The Hyland scientist suggested a visit to see if they could acquire the technology. Watson was agreeable and took them on a tour of his laboratory. "He gave a demonstration," says Greene. "He showed us how to do the fusion, and plate out the cells, and purify the ascites, and so on and so forth. And nothing looked particularly magical. So, we retired to the student union there at UCI and after about the second pitcher of beer, we decided, 'We're going to start a company.'"[23]

During his time at Hyland, Greene had learned a lot about antiserum and diagnostics markets. He knew enough to recognize that hybridoma technology and monoclonal antibodies could shake them up considerably. The technology was in the

[23] The magic didn't inhere in the technique itself, as Greene saw. For cell biologists, the procedure was unremarkable (although cell fusion was certainly an art and achieving success in it required a good deal of inarticulable skill derived from practice and not from a book). The magic of hybridoma technology was socially generated. It was created by sleight of hand – by drawing attention away from the mundane nature of the science and getting people excited about the possible applications of monoclonal antibodies. Walt Desmond, who worked in Hybritech's cell biology program performing fusions and creating large antibody libraries, says "You know, I used to say that the biggest secret was that there was no secret."

public domain, but he knew of no companies moving to exploit it. He had been working in the immunodiagnostics business for several years, and hadn't before heard a peep about hybridomas or monoclonals in any outfit's development plans. He hadn't learned of the breakthrough himself until he happened to hear Bill Dryer, the academic, speak. It appeared to Greene that he was dealing with a purely academic phenomenon, and that he had stumbled onto a genuine opportunity before anyone else in commercial diagnostics. He had access to the required cells, he had a couple of immunologists on board, and he was excited about the idea, but before committing any of his personal resources to the project, he went to seek advice from his dad. His father had gone into business for himself several years earlier after Celanese had decided to move its synthetic fiber operation to New York City. His dad was invited to move again with the division, as he had before from Ohio to North Carolina, but this time, says Greene:

> His reaction was 'Hell, no.' He decided that the only thing to do was to start his own business. I was just out of Harvard, working with McKinsey, and I ended up helping him analyze businesses, balance sheets and so forth. He ended up buying a small distributor of fiberglass products for the boating industry in Fort Lauderdale. You know, his point of view was, 'I want to live in Fort Lauderdale, I love boating,' and for the next two years, three years, he and my mother struggled with all of the classic small business problems. You know, deadbeats who buy a bunch of stuff and don't pay, employee problems, and so on. By the time Baxter gave me my walking papers, they had turned the corner. He was then the president of the Boat Builders Association in Broward County. I went to him and asked, 'Do you think I should start a business?' He said, 'Hell, I only wish I'd done it fifteen years sooner.' So that kind of greased the tracks.

Greene rented a bay in an industrial park down the street from the Hyland facility. He called it Cytex Laboratories. Hyland was shutting down and preparing to

vacate its building. The firm was holding a fire sale to liquidate furnishings and supplies on the premises, so Greene and his partners began purchasing benches, hoods, and laboratory equipment at book cost. Greene then put together a business plan for the new company. He intended to drum up investments and business by approaching major diagnostics companies and proposing to develop antibodies for them to use in their existing assay systems: "We decided that what we needed to do was get good at making these antibodies and do it for others and sell them on a contract basis." Greene was developing a pitch that would portray hybridoma technology as a revolutionary development, one that would initially produce better antiserum, but one that might also serve as the basis for a fundamentally different way of manufacturing immunodiagnostics. He intended to inform the giants of the industry that hybridoma technology "is going to change everything, and if you guys want to be at the lead, we can help you do that."

The thought of seeking out venture capitalists never crossed his mind. He had never heard of venture capital. The venture capital industry, as it is organized today, didn't begin to take shape until the late 1960s. There was no talk about venture capital as a financial instrument at the Harvard Business School when Greene was there. During those years, the specific investment principles and concepts of risk management that characterize the venture capital industry today were just being put into practice for the first time, in places far removed from the Fortune 500 executive suites and boardrooms that Harvard MBAs were being groomed to enter. Naturally, Greene understood that there were some wealthy individuals and private foundations that made risk capital available to entrepreneurs, some investment banks that tolerated

higher degrees of uncertainty than others, and a few SBICs and proto-venture investment groups like the American Research & Development Corp. in operation, but until the 1960s, there were no firms raising venture funds from large institutional investors.[24] Ignorant of venture capital, Greene anticipated soliciting support from more traditional sources.

The first big company that he called on was Beckman Instruments, which had actually advertised for innovative proposals from entrepreneurs. A large segment of Beckman's business resembled Hyland's – the sale of diagnostic products (assays, reagents, instrumentation, etc.) to clinical reference laboratories, hospitals, physicians' offices, and so on. Greene gave his presentation, but his appeal didn't generate much interest: "They all listened politely, and then kind of shook their heads like, you know, this guy's crazy." The prospective entrepreneur hoped for a warmer reception at his next stop, Syntex, a pharmaceutical company located in Palo Alto, California. Syntex had a reputation for being innovative and science-driven. Greene admired the company because it was the only significant entrepreneurial success story in the North American pharmaceutical industry since the 19th century. It was founded in 1945 in a small town outside Mexico City, by a chemist from Rockefeller University named Russell Marker. Marker had been working in the area digging up Mexican yams. Known as barasco, the plant was a rich source of diosgenin, a plant steroid. Marker had developed a method processing diosgenin as a starting material for the synthesis of the hormone progesterone. Progesterone was used as a treatment for endocrine disorders. At the time, it was a very valuable commodity, selling for more than $100

[24] See chapter four, pp. 311-329, for an abridged history of the venture capital industry.

per gram. Syntex began by manufacturing synthetic progesterone, and eventually, under the direction of Carl Djerassi, carved out a niche in pharmaceuticals by producing a variety of medicinal steroids, including synthetic cortisone and norethindrone, a synthetic variant of progesterone that suppresses ovulation. Norethindrone was a major commercial success when marketed in the 1960s as a birth control pill, the second to reach pharmacies.[25]

In 1961, the firm had grown to the point where it could establish a presence in the United States. It built a campus in the Stanford industrial park in Palo Alto, California. In 1966, Syntex financed the formation of a diagnostics subsidiary called Syva. By the time Greene approached the company in 1978, Syva was considered by most industry insiders to be on the leading edge of diagnostics technology. That reputation was earned mainly from the firm's introduction of enzyme-based immunodiagnostics and its development of homogeneous immunoassays – tests that eliminated the need for inconvenient and time-consuming antibody (or antigen, or sandwich) separation and washing procedures. Greene knew that Syntex had nurtured Syva as a start-up and hoped that the company would consider doing the same for Cytex upon hearing about the marvelous new cell hybridization technology that would enable him to manufacture reagents far superior to polyclonal antiserum. "I made this impassioned presentation to them," he says, "on how they should work with me, how I

[25] A brief history of Syntex is available in Arthur Kornberg, The Golden Helix: Inside Biotech Ventures, Sausalito, CA: University Science Books, 1995; ch. 3. The first oral contraceptive approved by the FDA was Searle's Enovid, in 1960. The product was shown to cause serious side effects, and the dose in the original formulation was drastically reduced. See Elizabeth Siegel Watkins, On the Pill: A Social History of Oral Contraceptives, 1950-1970, Baltimore, MD: Johns Hopkins University Press, 1998.

would supply them with antibodies, and how this would improve their product." He was disappointed when, at the end of his talk, the chief technical officer of Syva declared "'Monoclonal antibodies are an academic curiosity. They will never amount to anything.'"

ONE OF THE MOST IMPRESSIVE HUMAN BEINGS...

The announcement meant that Greene wouldn't be doing business with the Syva division, but he found out afterwards that the trip hadn't been a complete waste of time. A few corporate development people at Syntex, members of the group that in-licensed new technologies, wanted to hear more. They weren't particularly sophisticated when it came to antibodies and cellular immunology, Greene says, but they understood the concept and were intrigued by the marketing angles that he had presented: "They got real interested and started to talk equity." Negotiations with Syntex got underway, but as they progressed over the next few weeks, Greene received a call from a headhunter who wanted to talk to him about a marketing position at a small San Francisco company called Genentech. Greene had never heard of the firm – it was still just a tiny storefront operation at the time – but it sounded interesting since he was planning to embark on an entrepreneurial venture of his own. He decided that he had a lot to learn by checking it out, although he didn't intend to accept a job offer. He flew up to South San Francisco and spent a day with Bob Swanson.

Greene learned all about Genentech, and discussed the marketing position, but before flying home late in the afternoon, he admitted to Swanson that what he really wanted to do was to start his own business. He didn't divulge any details, but assured

Swanson that it had nothing to do with recombinant DNA: "I said, 'Don't worry. It's not competitive.' It's fine. But it's similar." That wasn't the end of it, however. Swanson liked Greene, and had another idea for him to consider: "That night he called me at my home and said, 'Well, you'd be great for our marketing job, but even better for something my partner Brook Byers is working on." Swanson told him about Byers' monoclonal antibody company that was already up and running in San Diego. Greene agreed to talk to the venture capitalist and then, he relates, "I called my partners in a panic. I said, 'Oh shit, we've got competition already.'" Byers called the next day to arrange a meeting. Greene was up in Orange County, and Byers was down in San Diego, so they met halfway in Oceanside, California for lunch. The two were the same age, and shared passions for science and business, so they hit it off. Greene had intended to remain discreet, but lunch turned into a two and a half-hour long conversation. Greene didn't tell Byers about Cytex, but he did enthusiastically reveal how much he already knew about monoclonal antibodies: "My problem is once I start talking, I can't stop." Byers called again the following day to discuss a possible invitation to join Hybritech. Greene thanked him, but told him that he was working on something else and had promised his partners that he wouldn't talk about it. Byers asked if it had to do with monoclonal antibodies. Greene told him that it did, and Byers suggested that they needed to talk some more.

Byers wanted Greene to meet his partners. "We decided to have a summit meeting," Greene says. "I was then living in a duplex on Balboa Island in Newport Beach and I said, 'Alright, let's have a meeting here and we'll see what's going on.'" Ivor Royston remembers getting a phone call from Byers: "He'd heard that there was

this guy up in Orange County who wanted to start a monoclonal antibody company, by the name of Ted Greene. They had been asked to look at some guy from Baxter. Well, it was Ted. Brook asked me to go up there with him to meet him, to see what he was planning to do." Greene invited his partner from Hyland, Royston and Birndorf drove up from La Jolla, and Byers and Tom Perkins flew in from San Francisco. Greene picked up the venture capitalists from the Orange County airport and drove them to his bayfront apartment. Perkins and Greene quickly got acquainted: "Tom is an avid yachtsman, and I'm into boating, so we walked out on the front porch and bonded. Brook finally had to say, 'Guys, we're here to have a business meeting. Get in here and stop talking boats.'"

The group discussed monoclonal antibodies, and, again, Greene couldn't contain his excitement about the subject. He let slip his antibody marketing plan, which resembled his approach to marketing the freeze-dried controls that he and Tom Adams had developed at Hyland. He explained that it would be a mistake to sell monoclonals cheap. Royston's business plan had proposed selling better antiserum for lower prices and dominating the market. Greene believed monoclonals should be positioned as a next stage technological breakthrough and sold at a premium: "You can use the technology to cut the price of things, or you can use the technology to go to new capabilities that you can charge a premium for. To this day, I'm convinced that when Perkins heard that, he went, 'Ah, there's a plan.'" Greene displayed his knack for marketing that day, and his flair for thinking creatively and thinking big, as well. The Hybritech group recognized that he was blessed with the qualities that make for an effective chief executive of a high technology venture. Royston recalls his

impression of Greene: "He was very personable. For a marketing guy, he was knowledgeable, he was intelligent. He was a good speaker, an articulate spokesman for the technology. So, he'd make a good outside person, to talk to outsiders." When the group huddled, Birndorf says, "We figured we could do two things by hiring him as president, one, kill a competitor, and two, get a seasoned industry guy."

An offer was extended, but Greene replied that he had partners and needed to talk to them. At the same time, Syntex was displaying sustained and increasing interest in the Cytex start-up and began pressing Greene for a commitment. To further complicate matters, Greene had begun to entertain doubts about his partners: "I was worried about the team that we put together. I was starting to have trouble with this scientist at Hyland who was going to be a big part of it. He was having trouble with the notion that I was going to be in charge. So, I was beginning to think, 'Oh, God, this is a rat's nest.'" Perkins then summoned Greene to San Francisco to visit the venture firm's offices at One Embarcadero Center. The conference began with Perkins explaining the venture capital business (according to Greene, Perkins once described his firm's first, but very successful, fund as a barrel full of piss with a couple of cherries floating in it – Tandem Computer and Genentech). Soon, Perkins steered the conversation toward Hybritech:

> Tom started turning the screws. I'll never forget it. It was sort of the killer meeting in his office in San Francisco, just the two of us. He sat me down in his office and said, 'Look, you can go ahead by yourself and start this business in Orange County, and I'm sure you'll do very well. From what I hear, you have a sound concept that will work.' But he said, 'We know how to build companies. We want to build a major pharmaceutical company. We think this idea is big. You know, we can help you raise money, we can help you recruit people, we can help get

> the right lawyers and the right accountants, we can help you build a really big company.

To top off his pitch, Perkins promised Greene that he would become famous: "He said, 'You'll be quoted in Business Week.'" Greene didn't know it at the time, but Perkins happened to be talking to the magazine later that day in order to promote another company in the firm's portfolio. Two months later, after accepting the Hybritech job, Greene was, in fact, interviewed and quoted by Business Week on Hybritech and the new phenomenon of biotechnology.[26] His Orange County partners were naturally disappointed, as was the corporate development team at Syntex, but Greene's decision turned on the fact that Brook Byers and Tom Perkins were standing behind Hybritech. The firm had two expert financiers and high tech managers guiding the operation from the boardroom: "Tom had made some points that were absolutely right. If you ask me 'What is the great value of professional venture capital?' That's where it's at. It's the experience, the knowledge to really help drive big ideas quickly toward fruition, really getting the talent, money, and the structural aspects of the business in place." So, Perkins had convinced him, and Greene decided that he would pack his bags and move down to San Diego. Ivor Royston believes that Greene was most attracted by the fact that Hybritech was already operational:

> He didn't have the cultures going, he didn't have the scientists, he just had the idea. We had everything up and running, and we had the venture capitalists. Kleiner-Perkins had already invested in us, and I think he saw the opportunity to come in and be the president of this

---

[26] "Venturing Into Medical Technology," Business Week, April 16, 1979: 107-108, 112. Greene said, "The diagnostics business is entering a new cycle. The last two decades have been a hardware oriented period, but the electronics technology is maturing and attention is shifting to cellular biology." On hybridoma technology, specifically, he remarked: "Our challenge is to take the technique and industrialize it."

> company, the CEO of this company, and fulfill his aspirations, and that's what happened.

Greene says as much himself. He was particularly impressed with the venture capital backing. Greene observed how much Perkins contributed to the company, and now identifies him as the driving force behind the Hybritech's success: "I think over the years at Hybritech, there were a number of points where he gave the company exactly the right strategic kick in the head, and he deserves a lot of the credit for how well that company did." Russ Curry was the company's first cell biologist. He left after just a few months because he didn't think the firm was going anywhere. Many years later, after conceding his error in judgment, he says, "The truth is that behind the scenes were some very expert people who guided Hybritech to success." He is talking about Tom Perkins. From the time Hybritech was founded until the day it was purchased by Eli Lilly, Perkins kept his hands firmly on the reigns of the company and strongly influenced its strategic direction. Greene says, "He was our chairman for seven years. At various times, Brook or I had the title, but at every board meeting, I used to coach the officers making the presentation – 'How about having a little eye contact with somebody else besides Perkins?' He dominated the intellectual activity of that board."

Perkins also encouraged Greene to recruit aggressively, to pursue very astute, very talented, and very experienced people for Hybritech's management team, even though the company was just a fledgling start-up and couldn't offer top flight executive compensation packages. Without that encouragement, Greene believes that he would have been "far more modest in the kinds of people that I would have

expected or targeted for this kind of an operation." But, emboldened by Perkins, Greene tried to hook the best available on the technical and business opportunities while asking them to take pay cuts, and then he'd send them to San Francisco: "I could run them through his office. After an hour with Tom Perkins, they were putty." Tom Perkins could hardly hope for a bigger fan than Ted Greene. Greene calls him "a visionary." "Once, I figured out," Greene relates, "that the best investment strategy you could follow would be just to buy stock in companies where Tom was chairman of the board. He is one of the most impressive human beings that I've ever had the privilege to work with." Hybritech might have had charismatic leadership sitting on its board of directors.

Ivor Royston also mentions his admiration for Tom Perkins, and the judgment he demonstrated in evaluating people, technologies, and business opportunities. Royston, along with many others, perceived special qualities in the venturer, qualities that might be bundled into an imputation of charisma:

> Tom Perkins, I think, was a very intuitive person. It's not like he had to do extensive due diligence, you know. Once he got comfortable with the technology, intuitively, and it made sense, and he got comfortable with the people, he was willing, basically, to bet on that, to bet on you. When they all [the partners of Kleiner Perkins] came down to visit our lab [Royston and Birndorf's] and we went to the airport, I remember it was Tom Perkins who said, 'I'll give you three hundred thousand.' It wasn't like today, you know, where all partners in a firm meet to discuss every company. For a guy to just go down to the airport and say, 'OK, let's do it,' you know, he clearly was the dominant person. I admire that kind of thing. I think more and more people should, instead of doing extensive due diligence, just trust their instincts, their gut, you know, 'Let's do it.' Because, in the end, you know, you can weigh all the risks, and there are always risks involved, and, in the end, it comes down to a very intuitive feeling about whether you want to invest or not. You're investing other people's money, but

> they've had a very good track record. And so, I admire Tom Perkins, and his intuitiveness.

A MAP OF THE FUTURE

The first item on Ted Greene's agenda when he joined Hybritech on March 1, 1979, was to formulate a new business plan for the firm. He needed to assess exactly where the company was in its research and development efforts, identify where it needed to go in order to become successful, and specify the means by which it intended to get there. Greene had to present a document to the board of directors (then comprised by Ivor Royston, Brook Byers, and Tom Perkins). During its first four and a half months in operation, the company had already spent half of the $300,000 in seed money provided by Kleiner Perkins. Howard Birndorf had been frugal. The money had been wisely allocated. The firm had an anti-hepatitis antibody to show for it. But Hybritech was still a long way from manufacturing products and generating revenues. Pulling out of the red, crossing the breakeven mark, and becoming profitable were events somewhere off in an uncertain future. In order to make further progress toward the goal of profitability, the company would shortly require a fresh infusion of cash, and appeals for investments would require justification. Greene would have to explain what Hybritech intended to do with any funds it received. This is why he wrote the new plan.

Ivor Royston's original business plan was a sketchy six-page letter to Brook Byers. Greene's document, by contrast, was a detailed report worthy of a Harvard MBA and McKinsey consultant. It totaled fifty-eight pages in length. It began with a brief summary that got right to the point – it encapsulated Greene's appraisal of the

state and capacities of the company, his forecast for one of its possible futures, and his implicit request for help from Kleiner Perkins, all in one sentence: "...this plan shows that Hybritech can reach breakeven by the end of 1980 on an equity base of $1,900,000." [27] Greene estimated that Hybritech would need to secure an additional $1.6 million, and at least some of it by July. The company was operating under conditions that all biotech firms to follow would have to learn to live with. There was never enough money. Hybritech was burning through its cash reserves at a rate that would leave it bankrupt in a matter of months, at a stage in its development when it needed to increase its expenditures in order to accomplish its technological and commercial goals. This is the way of things for research intensive commercial ventures without products to sell. Raising money is a perpetual concern and activity within such firms.

By contemporary venture capital standards, the $1.6 million that Greene was asking for was not extravagant. Venture capital underwent a massive expansion in the early 1980s, after the Silicon Valley pioneers of the industry, including Tom Perkins and Eugene Kleiner, had received huge returns on relatively small investments made in the previous decade. In 1978, the year Hybritech was founded, 23 venture capital funds were raised in the U.S. Together, they solicited $482 million. Just five years later, in 1983, 147 funds raised over $6 billion. The pool of available capital contracted after the stock market crash of 1987, and during the recession years of the early 1990s, but it then swelled again, becoming bigger than ever. The industry set records in the year 2000, before the dot.com bubble burst – 228 different funds

[27] Howard E. Greene, "Hybritech, Incorporated," May 1, 1979; p. 2.

collected nearly $70 billion to invest.[28] Kleiner Perkins' first fund in 1972 had totaled just $7 million, and that was spread among seventeen different firms. However, after the remarkable successes of Tandem Computer and Genentech from among that bunch, and after similar instances of massive wealth generation in a few other venture capital funds around the same time, the high-tech funding environment was radically transformed.[29]

In 1982, Kleiner Perkins raised a $150 million 'megafund.' By that point, the vast ocean of capital available to support high tech ventures had already inflated placement figures past the point of meaningful comparisons to earlier investments. The flood of money created a very different atmosphere, one in which aversions to risk were attenuated and allocations of venture capital in biotechnology were made in ways that seemed, in retrospect, to many industry veterans, almost indiscriminate. After the market downturn of 1987, biotech companies struggled to sustain themselves. The weakest were significantly devalued, and many newcomers to the venture capital business limped away, leaving their limited partners to fend for themselves. The survivors remembered the wisdom in their venture capital folk sayings – 'In a strong wind, even turkeys fly,' was one frequently repeated at the

---

[28] Paul A. Gompers and Josh Lerner, The Money of Invention: How Venture Capital Creates New Wealth, Boston, MA: Harvard Business School Press, 2001; p. 93.

[29] The returns to Kleiner Perkins' limited partners from the first $7 million fund w
ere stunning. The firm put $1.5 million into Tandem Computer, and the value of that placement rose above $250 million. The firm's total investment in Genentech was only $200,000, but, at one point, that stake was worth $83 million. Greene tells that when Genentech raised $35 million in the company's initial public stock offering, "Perkins was furious because he thought they that they had left a huge amount of money on the table. The pricing was right, they just didn't issue enough shares to satisfy the demand. They could have gotten seventy million, easy. So, six months later, Cetus comes to market and raises $100 million, and Tom could never get over that."

time.[30] Venturers tightened their belts for a time, until new capital flows attracted another wave of rookies to the business (but not necessarily to find commensurate numbers of strong new technologies or well-conceived new business plans), and valuations of unproven start-ups resumed their steep upward climb. Hybritech's early financing rounds predated all of these changes. The company's initial $300,000 seeding came out of KPCB's second fund, which totaled just $15 million. In 1979, Greene was operating in a different financial universe. The $1.6 million that he wanted to raise was modest considering what he was proposing to do with it, but for a risky technology investment at that time, it was a substantial amount of money.

The partners at Kleiner Perkins were sold on the idea of monoclonal antibodies, and after the success of the proof of principle experiments, they were ready to move forward. But before dedicating the kind of money that Greene estimated would be necessary to underwrite technical progress and organizational maturation and expansion at Hybritech, they wanted to see a map of the path the company intended to follow. And, on the second financing round, Kleiner Perkins intended to syndicate the investment, to bring other financiers in on the deal. For venturers, the purpose of syndication is to share the financial burden and risk, mainly, but also to validate technologies and companies, and to benefit from the due diligence and oversight of others.[31] Kleiner Perkins wanted it, so new investors had to be convinced. Greene needed to make a persuasive case. He wanted to show that, in fact, hybridoma

---

[30] David Coburn, "Stock Crash Crimps High-Tech Start-ups," San Diego Tribune, December 21, 1987.

[31] See Josh Lerner, "The Syndication of Venture Capital Investments," Financial Management 23, 1994: 16-27.

technology had generated real market opportunities to exploit and that Hybritech was positioned to take advantage of them. To do so, he incorporated elements of the sales pitch he had composed for Cytex Laboratories. After hearing about hybridoma technology from Bill Dryer, Greene had recognized, as had Ivor Royston a year before him, that it represented a technological paradigm shift in the antibody business. He knew, too, that conservatives in the industry would resist. For some, the costs of transitioning to the new approach would be high:

> This business of cell biology, cell fusions, plating, cloning, and so on, was unfamiliar. Immunologists, at that point in time, were people with cages full of rabbits and the techniques for developing antiserum were pretty well established. The guys who controlled it were the ones who were good at injecting rabbits and sheep, or horses, you know? And you were basically asking them to start over. It made obsolete anything they had ever done. So, they instinctively didn't like it.

Greene was certain, however, that hybridoma technology represented a significant breakthrough, and one that offered economic advantages sufficient to justify the costs associated with switching over from established methods. He likened the introduction of hybridoma technology in the diagnostics business to the introduction of large-scale integrated circuits in electronics. He expected the development to "encourage the emergence of a new industry of companies."[32] Greene firmly believed that a technological revolution was at hand, and that the diagnostics industry was on the verge of going monoclonal. The business proposed in his plan for Cytex Laboratories had entailed selling customized antibodies to immunodiagnostics manufacturers. He expected these firms to recognize the advantages of monoclonals, and he was confident that he would be able to drum up interest in the antibodies he

intended to produce. He believed that possession of the new technology and expertise in applying it would support the formation of new entrepreneurial ventures.

After joining Hybritech, Greene became privy to evidence that supported his hypothesis. His new business plan for Hybritech included an exhibit listing companies that had contacted the firm to express interest in becoming customers. The start-up was less than six months old, but no major diagnostics manufacturer (save Johnson & Johnson's Ortho subsidiary) had failed to inquire about purchasing one or another of the firm's monoclonal antibodies. Included on the list were Abbott, Becton Dickinson, Bio-Rad, Behring, Corning Diagnostics, Coulter, Dow Diagnostics, Miles, New England Nuclear, Nuclear Medical Labs, Pfizer Diagnostics, Pharmacia, Syva, and Technicon. These companies had only just heard of Köhler and Milstein and Hybritech. They hadn't experimented with monoclonal antibodies, and no one knew for sure how they would perform as reagents, but it was clear enough that a market was beginning to coalesce. Hybritech, however, wasn't planning to make the sale of commodity reagents its principal business, at least not for long. The venture capitalists were pushing the firm to challenge the industry's dominant corporations in the manufacture of diagnostic immunoassays, and, as Tom Perkins had explained to Greene in San Francisco, beyond this, entry into the pharmaceutical business was the ultimate goal.

Greene had to explain how Hybritech was going to get there. He began by elucidating the technology. The first section of the plan provided basic lessons on immunology, the properties of immunoglobulins, and conventional medical and

---

[32] Greene, "Hybritech Incorporated," p. 13.

industrial uses of antibodies – as reagents in diagnostic tests, as therapeutics (in antivenin or antitoxin preparations used for passive immunization, for example), and as components of immunoadsorbents employed in the purification of biological substances. Greene then described the production of conventional polyclonal antiserum – which he had elsewhere disparaged as "an uncontrollable black art" – and introduced hybridoma technology in contrast.[33] The next section presented an analysis of markets for monoclonal antibodies in diagnostics, therapeutics, research, and industrial processes. Greene explained that diagnostic markets had been growing following recent technological advances (the invention of radioimmunoassays, for example). Better diagnostic technologies meant improvements in both the quality and efficiency of medical care, and market recognition of the fact had led to rapidly ballooning demand. "In 1978," Greene reported, "the U.S. market for clinical diagnostic reagents alone – excluding instrumentation and commodity supplies (e.g., test tubes, paper towels, etc.) – exceeded $1.1 billion, an increase of 18% over 1977 sales."[34] He expected the market to double in size in five years, and he predicted that sales of new immunodiagnostic products (reagents, assay kits, and instruments) would grow at even faster rates.

The plan went on to enumerate the advantages of hybridoma technology and monoclonal antibodies in the manufacture of immunodiagnostic products. Cell hybridization promised to be a cheaper method of producing antibodies than bleeding animals and purifying antiserum. It also promised to deliver reliable, continuous

---

[33] "Venturing Into Medical Technology," Business Week, April 16, 1979; pp. 107-108, 112.

[34] Greene, "Hybritech, Incorporated," p. 14.

supplies of standardized reagents that were previously unavailable. Researchers expected to be able to select monoclonal antibodies exhibiting greater specificities and lower rates of cross-reactivity than polyclonal mixtures, and the affinity of monoclonals for specific antigenic targets meant that diagnostic tests could be designed with greater signal-to-noise ratios and increased sensitivity. Monoclonals would likely permit the design of assays to differentiate many analytes that, due to their molecular homogeneity, defeated the capacities of conventional polyclonal antisera to distinguish them. (e.g., normal and cancerous cells in the same tissues, or individual members of steroid, hormone, or isoenzyme families). Monoclonals might also serve, eventually, as radiolabeled tracers to improve in vivo imaging techniques. In addition, Greene suggested that, as a new kind of reagent, monoclonal antibodies would probably stimulate the invention of new kinds of analyte detection systems, including non-isotopic assay formats.

The existing market for therapeutic antibodies in 1978 was much smaller than for diagnostic immunoglobulins – only $31.8 million in the U.S. – but Greene asserted that "the most exciting market opportunity for monoclonal antibodies lies in their potential for therapy in the treatment of diseases."[35] Medical researchers like Ivor Royston hoped that exogenous antibodies could be employed to trick the immune system into ignoring the self/not-self recognition processes that presumably prevent it from attacking cancerous cells, or to trigger immune responses against pathogens when, for one reason or another, patients did not mount their own defenses. They also saw possibilities for deploying monoclonals in chemical warfare against cancers, as

high precision delivery vehicles for chemotherapeutic agents. In theory, due to their fine specificity, the antibodies would carry toxic payloads to tumors selectively, with pinpoint accuracy, while sparing normal tissues from damage. Another idea was to employ monoclonal antibodies as immunoadsorbents in dialysis-like ex-corporeal extractions of toxic substances from blood.

Greene added a cautionary note: development times would certainly be lengthier for therapeutic antibody products, and development costs considerably higher, because of formidable technical and regulatory hurdles associated with the manufacture and clinical testing of in vivo products. He then briefly mentioned possible non-medical industrial applications – monoclonals might, for instance, be employed to improve many different kinds of purification procedures, especially in the chemical and food industries. To conclude his analysis of market opportunities, Greene discussed anticipated demand from life scientists for specialized and standardized antibodies to employ as tools in biological and biochemical research. He argued that while the size of this market would probably remain limited – no more than 10% of the in vitro diagnostics market was his guess – it displayed certain attractive features nonetheless:

> Although its direct profit potential is limited by the market size, the research market nevertheless represents an important source of new product ideas, professional collaboration, and credibility for suppliers. It also represents a market segment with virtually no regulatory constraints, low marketing and distribution costs, and – accordingly – high net margins.[36]

---

[35] Greene, "Hybritech, Incorporated," p. 19.

[36] Greene, "Hybritech, Incorporated," p. 21.

Greene followed his market analysis with a review of the competition. Having made his case for the reality of sizable markets for monoclonal antibody products, he tried to show that Hybritech was in a position to exploit them and outperform competitors. He argued that, despite its small size and undercapitalization, Hybritech would be able to prosper and grow by designing, manufacturing, and marketing monoclonal products. Greene focused on diagnostics, because pharmaceutical companies had not yet acquired hybridoma technology, and, at the time, no one in the health care industry expected them to display any interest in doing so. Cell biology was a foreign culture. Pharmaceutical development was the province of chemists. Big Pharma didn't truck with the experimental methods of biologists, and especially not with esoteric techniques like cell hybridization.[37] Medicinal chemists worked with small molecules; they didn't know what to do with huge (relatively speaking) polypeptides like antibodies. In 1979, making projections about competition in markets for revolutionary antibody therapies was an exercise in pure speculation. Greene elected to skip it. Hybritech couldn't afford to develop a full-scale therapeutics research program, anyway, at this early stage in its development. As Kleiner Perkins had insisted from the beginning, the new venture was first going into the diagnostics business.

---

[37] A number of large pharmaceutical corporations had biologics divisions that employed standard techniques to produce vaccines and antiserum products. Merck was far and away the industry leader, but, as was the case elsewhere, the revenues generated by its vaccine business were dwarfed by those brought in by the company's roster of blockbuster compounds. See Louis Galambos and Jane Eliot Sewell, Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme and Mulford, 1895-1995, New York: Cambridge University Press, 1995.

Greene had observed that recent technical innovations in diagnostics had been introduced by entrepreneurial start-ups, and that these firms had been able to capture substantial shares of certain niche markets. He gave some examples: Syva was marketing the first enzyme immunoassays; a company called Nuclear Medical Labs had successfully introduced a new thyroid test system; Clinical Assays had developed a novel coated tube solid-phase radioimmunoassay format; and Johnston Labs was selling a popular new microbiology instrument. Syva was a division of Syntex, and the other three had been recently acquired by large corporations in the industry – by Warner Lambert, Baxter Travenol, and Becton Dickinson, respectively. This was how innovation was organized in diagnostics. Greene expected the trend to continue with the introduction of monoclonal antibodies: "Start-up companies organized expressly for the purpose of commercializing hybridomas will probably lead in bringing this technology to market."[38] The difference with hybridoma technology, however, according to Greene, would be the breadth of its impact. It had the potential to transform immunodiagnostics at a fundamental level – both technically and organizationally. Hybridoma technology, Greene reasoned, could enable a small company to compete on an even footing with the giants of the industry:

> A few large, rich companies will spend their way – brute force – into hybridoma expertise. Abbott, Beckman, Syva, Becton Dickinson, Baxter, and Johnson & Johnson already appear to be headed this way. Meanwhile, the diagnostic divisions of the first five of these have already approached Hybritech to do joint development, presumably as a hedge against 'corporate' failure. This hedging on the part of divisional personnel reflects the rather dismal record of real technical innovation displayed by the large pharmaceutical and instrument companies. Undoubtedly several of their R&D projects will come to

[38] Greene, "Hybritech, Incorporated," p. 27.

> some sort of fruition, but nothing indicates that the large, mature companies will present any meaningful obstacles to reasonable market penetration by less ponderous newcomers.[39]

Greene believed that, in the struggle for control of monoclonal antibodies in the diagnostics industry, the smart, lean, and agile would prevail. The odds-maker was asking the venture capitalists to place their bets: "The most likely winners in this contest – based on past behavior in diagnostics markets and on the unique technical requirements of hybridomas – will be well financed, technically sophisticated, and operationally aggressive start-up ventures."[40] This, of course, was Greene's idealized description of Hybritech. He announced that "Hybritech intends to maintain a lean, flexible organization capable of moving quickly and decisively."[41] He wanted to build a company that could sustain innovative progress over time in a dynamic environment. The big firms suffered from procedural ossification, but Greene believed that a small outfit like Hybritech could avoid this condition. Beyond this, he had some ideas about why, in the race to profit from hybridoma technology, Hybritech, specifically, was the horse to back.

First, he noted, Hybritech had a head start. It had bolted from the gate several months ahead of Centocor, the next monoclonal company to appear on the scene. In fact, Greene had completed his revised business plan for Hybritech before Centocor was officially incorporated. The Hybritech team knew that their counterparts at Centocor were capable, because they were affiliated with the Wistar Institute, but they

---

[39] Greene, "Hybritech, Incorporated," p. 25.

[40] Greene, "Hybritech, Incorporated," p. 27.

[41] Greene, "Hybritech, Incorporated," p. 31.

believed that they could maintain their lead, and there was bound to be room for both in the diagnostics market, in any event. Second, Hybritech was putting together a superb team of researchers and scientific advisors – Greene was impressed with Ivor Royston, Gary David, and Russ Curry. Hybritech's science was cutting-edge, and the company anticipated attracting more top-notch researchers to its operation. Third, said Greene, the company had already developed its own effective fusion, clonal expansion, and antibody screening techniques as trade secrets. In fact, Hybritech was relying on known hybridoma protocols, for the most part, and on Sevier, Wang, and David's semi-automated solid-phase immunoassay for screening. That procedure had already been published, but it was true that the labs were busy learning by doing, ironing out bugs, and making incremental improvements in the company's methods.

Fourth, Greene mentioned Kleiner Perkins's commitment to the project. The venture capitalists were evidently in for the long haul. Greene was convinced that they wouldn't let the company founder unless confronted by some catastrophic technical or commercial failure, and he considered the business expertise lent to the firm by Perkins and Byers to be nonpareil. The fifth unique advantage enjoyed by Hybritech, in Greene's estimation, was its location in San Diego. The funds of knowledge, potential collaborators, and supply of qualified technical workers available at the city's world-class academic institutions – UCSD, Salk, and Scripps – made the local environment an ideal one for a science-dependent start-up. (And, although he didn't mention it in the business plan, the climate and the image of the city as a place with an unusually high quality of life would aid tremendously in the recruitment of scientific and managerial personnel). Finally, Greene noted that Hybritech's

independence would permit it to enter into beneficial joint research and marketing ventures with major pharmaceutical and diagnostics companies. Because it held a technological lead, the company was bound to receive offers for deals that would enable it to accelerate its march toward profitability. For all of these reasons, Greene argued, Hybritech was a good bet and a sound investment.

MAKING PROJECTIONS AND MAKING MAGIC

Greene then continued on to articulate a strategy for securing and steadily gaining shares of markets for research antibodies, diagnostic assays, and in vivo imaging and therapeutic products. He envisioned the company passing through three successive phases of growth. Hybritech was already embarked on the first phase – "development." The firm was concentrated on controlling, streamlining, and routinizing hybridoma and antibody production. The next step was to manufacture antibodies in bulk for sale to researchers and diagnostic test manufacturers, in order to generate the company's first revenues. Initial development costs would be high, but manufacturing and marketing expenses would be low. Greene's scheme predicted gross margins (ratios of gross profits to sales revenues) of 80% using hybridoma techniques, and forecast that antibody sales would bring the company to profitability in the fourth quarter of 1980, even as research and development, marketing, and administrative expenditures increased substantially.

The second phase, which Greene labeled "initial growth," was to include the design and manufacture of monoclonal antibody-based immunoassay diagnostic kits. The first antigens selected as targets would be those for which monoclonal-based assays would offer clear improvements in performance over conventional tests (the

plan cited tumor cell surface antigens, isoenzymes and serum proteints, bacterial and viral antigens, and steroids and hormones), or those for which no immunoassays were available because of the limitations – too much cross-reactivity and insufficient specificity – of conventional antisera (e.g., molecular markers of breast cancer, prostate cancer, and fetal distress). Income from second phase diagnostic products would be used to fund research and development on therapeutic products, and to leverage Hybritech's entry into the pharmaceutical industry. Greene projected that revenues from second phase products would grow from $2 million in 1980 to nearly $50 million in 1984 – a very modest piece (about 2%) of what Greene believed would grow into a vast worldwide market – with profits sufficient to fund further technological innovation.

Greene expected that when Hybritech moved into the third phase of the master plan, "maturity," competitors would be pressing the firm in diagnostic markets with a variety of high-quality monoclonal-based products. "However, by this time," he wrote, "Hybritech will be a multi-million dollar corporation with the leading technical effort and the largest share of the market."[42] Upon achieving this level of commercial success, the company's objectives would be to maintain and extend its technological lead: "Hybritech strategy will then be focused on keeping ahead."[43] Greene anticipated that the success of the firm would enable it to support expanded R&D programs directed toward the design of the new in vitro immunoassays formats, new products for in vivo tumor and organ mapping, and antibody therapies of various kinds

[42] Greene, "Hybritech, Incorporated," p. 35.

[43] Greene, "Hybritech, Incorporated," p. 35.

for various diseases and conditions. Also on the R&D agenda were plans to generate human monoclonal antibodies from fusions involving human myeloma parent cells. These would replace murine antibodies for in vivo applications. A further area of development would be uses of monoclonal antibodies in chemical separation and purification processes – immunoaffinity chromatography, for example.[44]

Greene's revised business plan for Hybritech was boldly optimistic. It forecast after tax profits of $7 million for the company by 1984, and stated that "this profit level would support an equity value well in excess in of $100 million." These prognostications depicted a firm skyrocketing in value over the first few years of its career. Particularly brash were Greene's statements regarding the formation and progress of a pharmaceutical program at Hybritech. While acknowledging that timelines and costs for product development activities, clinical trials, regulatory reviews, and manufacturing set-ups would be significantly extended for in vivo diagnostics and therapeutics, Greene simultaneously announced that "Hybritech expects revenues from therapeutic products to begin during 1984."[45] It is not clear exactly what kind of products Greene had in mind, but he maintained that the firm's operating expenses would stabilize by 1984 at levels consistent with successful diagnostics companies. He predicted that beyond this point in time, just five years out,

---

[44] Column chromatography – the most common format – separates components of a mixture in solution by passing the solution through solid phase materials, e.g, gels, polysaccharides like cellulose or agarose, or silica, packed into a column. The components to be separated can be filtered by molecular size (large or small molecules find their way through with greater rapidity, depending on the material, and exit the column first) or adsorbed on the solid phase by specific binding acitivity or net electric charge, and then washed out of the column. Immunoaffinity chromatography employs antibodies as immunoadsorbents to bind target substances.

[45] Greene, "Hybritech, Incorporated," p. 36.

the economics of therapeutic drug marketing would begin to govern the firm's expenditures and strategic planning.[46] Greene was suggesting strongly that hybridoma technology and monoclonal antibodies would enable Hybritech to accomplish something that, for many decades, only Syntex had managed – entry into pharmaceutical markets as an entrepreneurial start-up.

Pharmaceutical companies in the 1970s were firmly entrenched corporate behemoths with the deepest of pockets. They had to be organizations of this kind in order to withstand the intense institutional and economic pressures that defined the industry. Pharmaceutical production had been a business exclusive to the rich and powerful ever since it had become scientific in the early decades of the 20th century. And when, in 1962 (after Syntex had established itself in Palo Alto), the Kefauver-Harris Drug Amendments had required drug makers to demonstrate the efficacy of their products prior to marketing, it became more capital-intensive than ever. The added regulatory burdens significantly lengthened the time required to take a chemical compound or biological molecule from discovery to market approval as a therapeutic product. By the 1970s, moving a new drug candidate through the arduous process of pre-clinical development, clinical testing, and regulatory review and approval took 11.6 years, on average.[47] By 1975, drug makers could plan to lay out $138 million, on

---

[46] Greene, "Hybritech, Incorporated," p. 60. Hybritech never came close to marketing a therapeutic product, but many in the company had faith in hybridoma technology and, from the beginning, expected to be successful in diagnostics. Gary David says, "I think we were all skeptical of the market projections, the five-year projections, which we actually came damn close to making. Maybe we even made them, I'm not sure. But we knew it was a hot item."

[47] Joseph A. DiMasi, "New Drug Development in the United States, 1963 to 1999," Clinical Pharmacology and Therapeutics, 69, 5, 2001: 286-296. The average development timeline grew to 14.1 years in the 1980s, and 14.2 in the 1990s. The slight increase in the 1990s reflected extended pre-clinical research periods. Two pieces of congressional legislation – the Prescription Drug User Fee Act

average, in order to see a single candidate drug or biopharmaceutical approved for marketing.[48] The revenue streams that Greene forecast in his Hybritech business plan didn't come close to generating this kind of money. He was making fantastic claims for monoclonal antibodies. He deemed their potential in diagnostics to be "exceptional," and, in therapeutics, "truly extraordinary." He was saying, in effect, that hybridoma technology was revolutionary, and that it would liberate Hybritech from Big Pharma's tyrannical economies of scale.

There were yawning gaps in the logic of Greene's arguments. In several spots, Greene provided no evidence whatsoever to support claims central to the rational assessment of the investment opportunity. Throughout, he presented the commercial success of hybridoma technology and the start-up as nearly sure things. The company was attempting to tackle difficult technical and commercial challenges with unproven scientific techniques, but the plan took progress for granted. It outlined the established facts about hybridoma technology in the manner of a textbook presentation, and

---

of 1992 and the 1997 FDA Modernization Act – led to declines in the average duration of clinical testing gauntlets in the 1990s (from 9 years in the previous decade to 8.6), and in the FDA review and approval process (from 2.8 years to 1.6 years). The Prescription Drug User Fee Act generated funds with which the FDA hired more reviewers and revamped approval processes for greater efficiency. The FDA Modernization Act established streamlined clinical testing and analysis protocols for new drug candidates, and expedited approval procedures for experimental treatments of serious, life-threatening, and rare diseases.

[48] The average cost rose to $231 million by 1991, and up to $802 million in 2000. See Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," Journal of Health Economics 22, 2003: 151-185; Joseph A. DiMasi, "New Drug Development in the United States, 1963 to 1999," Clinical Pharmacology and Therapeutics, 69, 5, 2001: 286-296; Joseph A. DiMasi, Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna, Journal of Health Economics 10, 1991: 107-142; U.S. Congress, Office of Technology Assessment, Pharmaceutical R&D: Costs, Risks, and Rewards, OTA-H-522, Washington, D.C.: U.S. Government Printing Office, 1993. A 2003 news release from the Tufts University Center for the Study of Drug Development calculated an average total outlay of $897 million per new drug when including post-marketing testing expenses. All of the analyses above are based on data compiled by the Tufts Center. Skeptics have suggested that Tufts' figures are over-inflated because the Center's compilations have relied on information supplied by manufacturers.

downplayed the significance of unknowns. It treated the company's laboratories as 'black boxes' – if sufficient funds went in one door, Greene promised, then medical products, revenues, and profits would come out another.[49] Yet, the company had, by the spring of 1979, produced only a single hepatitis antibody. That accomplishment was not going to earn the firm very much in the way of revenues or distinguish it as an industry leader in diagnostics, let alone pharmaceuticals. Hybritech was proposing to travel a long distance through two intensely competitive industries. Hazards and uncertainties lurked at every turn, but doubts and questions about road conditions and the practical efficacy of the firm's technology platform had been erased from Greene's business plan. For all of the numbers that Greene worked up in his financial projections, he neglected to estimate the odds that the technology and the company might fail. He was asking investors to take great leaps of faith.

The SEC requires, by law, that every public stock offering prospectus list the risk factors associated with a particular investment – e.g., uncertainties regarding technological progress, regulatory constraints, competition, market volatility, legal rulings on intellectual property matters, and so on. Greene's document didn't discuss any of these risks, as it might have, as a courtesy to the private investors that the plan was intended to attract. Greene didn't factor into his calculations any possible recalcitrance of biology toward Hybritech's ambitious plan. Nowhere did he consider how the company might be impeded or adversely affected by technological or clinical

---

[49] On 'textbook' portrayals of scientific knowledge, see Thomas S. Kuhn, The Structure of Scientific Revolutions, Chicago: University of Chicago Press, 1970 [1962]. On the 'black boxing' of scientific work, see Bruno Latour, Science in Action: How to Follow Scientists and Engineers Through Society, Cambridge, MA: Harvard University Press, 1987.

failures. The plan asserted without evidence or argumentation that Hybritech would be able to maintain its technological lead, and that competitors would not outperform it. Greene ignored the possibility that it might make good economic sense to sell Hybritech to a larger competitor if the start-up managed to generate some substantial value. For some time, that had been the fate of small, innovative companies in the diagnostics industry, but Greene elected not to address the issue. His business plan promoted the notion that Hybritech could establish itself as an independent manufacturer and marketer of therapeutic products. It didn't contemplate what might happen should complications arise, and it didn't consider contingency plans. But the omissions weren't oversights.

The scientific, commercial, and financial projections in Greene's document aren't properly read as a set of literal predictions. They should be interpreted, instead, as attempts to persuade his audience that Hybritech could succeed, that all the elements necessary for success were in place, and that the firm deserved the assistance and attention of financiers as much as any other. Greene was telling the venture capitalists what they wanted to hear. They needed companies that could become worth $100 million. They generally didn't invest in outfits that, according to their analyses, lacked the potential to reach this lofty plateau. Greene was attempting to convince them that Hybritech had the right stuff. He maintained that because Hybritech possessed the capacity to make monoclonal antibodies, it would be able to accomplish great things as a commercial venture. Greene couldn't prove this. He couldn't prove anything about hybridoma technology and monoclonal antibodies. But his projections weren't designed to prove or demonstrate. They were designed to

persuade. They were intended to foster confidence and generate faith in hybridoma technology and the company utilizing it. Greene didn't mention any of the various things that could go wrong for Hybritech because there was no point in it, and no need.

The venture capitalists understood the risks attending high-tech start-ups. They knew that failure rates were high. It was their business to know. Brook Byers had learned all about the promise and perils of biotechnology in the due diligence phase, and Kleiner Perkins had been studying the pharmacetucial industry for five years, ever since Bob Swanson had approached them with his idea for Genentech. New investors in subsequent financing rounds would naturally conduct their own risk assessments. So, the venture capitalists didn't want to hear about all of the hazards and uncertainties confronting Hybritech, many of which would be beyond the control of the company's scientists and executives (and Greene understood that discussing problems in the business plan would just provide investors with handy excuses to back out). The financiers wanted to know whether the company was on track, and whether the people in charge of it understood the direction in which they should be heading. They wanted know whether the company's management team understood that their number one job was to make the firm valuable – in order to make money for the venture capitalists. They wanted to know whether the people at Hybritech understood what would count as success.

The business plan demonstrated that Greene did understand. As he was promoting the technology and the company, Greene was, in fact, promoting himself and other individuals involved in the organization in various capacities. In order to

reassure potential investors that the technology was sound and that the company knew what to do with it, Greene included professional biographies of the company's principals that amounted, essentially, to long lists of credentials, affiliations, and awards. When investors read about Greene, Byers, Royston, Birndorf, David, and Curry, they learned that the company's research and development efforts were being led by two MBAs, two Ph.D.s, an M.D., and an M.S. The holders of these degrees had been associated with several prestigious scientific and medical institutions, including Harvard, Johns Hopkins, Stanford, UCSD, the Salk Institute, City of Hope, and Scripps, and a few notable non-profit charitable and governmental organizations, as well, including, the American Cancer Society, the Leukemia Society, the National Academy of Sciences, the National Institutes of Health, and the Veterans Administration. Greene was saying, in other words, that if these well known, highly regarded institutions and organizations recognized the quality of the Hybritech team, then potential investors should, too, and that, if anybody could make hybridoma technology a commercial success, this group could.

Greene also wanted and needed to convince potential investors that the leadership of the firm understood venture capital, the conditions and dynamics of the diagnostics and pharmaceutical industries, and the process of high tech innovation. The fact that he and Byers, the firm's two chief executives, had attended and held graduate degrees from the Harvard and Stanford business schools, respectively, helped to establish credibility in this regard. So did his association and experience with McKinsey, his record at Baxter and Hyland, and Kleiner Perkins' involvement with the company. Greene's market analyses, development strategies and financial

projections were then important for confirming and reinforcing the image of executive and managerial quality that he was attempting to generate for the firm. The substance was not critical as long as the specific ideas and numbers didn't sail too far off the coast of plausibility. Much more important was the form of the document. The revised Hybritech business plan was evidently produced by someone who was knowledgeable, creative, energetic, and resourceful, and who, further, was acquainted in a sophisticated way with business accounting procedures and the conventional tools of financial analysis and decision-making. Greene was hyping monoclonal antibodies by hyping his own abilities. Hybridoma technology was in its infancy and had no record of commercial success. It couldn't speak for itself. If it were to attract funding, then people would have to speak for it, and they would have to establish some credibility. Greene's task of selling science and technology was inseparable from the task of selling himself and his organization. Ivor Royston relates what has become common wisdom in high tech fields like biotechnology – venture capitalists invest in people not things:

> The idea is that if you invest in the right people and the technology doesn't work, then the people will find new technology, whereas if you have good technology and the wrong people, the technology can really flounder, and I've seen a number of examples of that. I've heard of a number of others. You can have some excellent technology, but the people can really screw it up. And sometimes, that technology never actually comes out, it never finds a place. So yeah, you invest in people over technology, but if you're investing in a technology company, what you want, of course, is a coming together of the right people with the right technology, and then you'll have a winner.

Ted Greene was astute enough to recognize the fundamental principles of the technology investment game. Although he was just learning about venture capital, he

understood right away what made start-up projects attractive (or not) to investors, and he zeroed in immediately on the ways in which venture capitalists evaluate business plans and determine whether the elements for success are present in an investment opportunity. He displayed a knack for saying the right things in the right ways. And his business plan produced the desired effect. In July of 1979, Kleiner Perkins purchased an additional block of 900,000 shares in Hybritech for $1.00 each. Sutter Hill Ventures also bought into the company in this second financing round. The Palo Alto firm purchased 500,000 shares at the same price, and placed a representative, David L. Anderson, on Hybritech's board of directors. The company now had enough money to continue on its way, to expand its scientific operation, and to start preparing an antibody product for the market.

Greene had become a champion of hybridoma technology and monoclonal antibodies, and had made himself indispensable to Hybritech. In the twenty-five years since Hybritech was founded, Howard Birndorf has become involved in numerous biotech companies as an entrepreneur, consultant, or intermediary. He has witnessed the process of firm formation many times, and suggests that, in the first instance, young start-ups and unproven technologies require champions to help them get off the ground. They need talented communicators who can tell their stories in ways that will persuade people with resources to get involved and support them. And what good storytellers need, above all, in order to do this effectively, from Birndorf's point of view, is conviction:

> First, you've got to believe that the science works, because if you don't see what the science can do, and you don't firmly believe...I mean, some people have said, 'If you put together the right team, it doesn't

> matter what they're doing. They'll make it work, even if the original stuff doesn't, they'll find something that does.' And that's probably true. But from my point of view, I always start with the science, and if I believe in it, then I can raise the money because I can tell a good story to the investors.

Dick Schneider is a Southern California venture capitalist who, although he did not invest in Hybritech, has many ties to the expansive social network that grew up around the company in San Diego. He knows Greene as a great believer in biotechnologies. He has observed him at work for a long time. He describes Greene as someone who knows how to convey his convictions in a manner that turns people on and not off – his presentations are engaging, enlightening, and entertaining, and his optimism is infectious. As Schneider tells it, Greene is zealous and enthusiastic, and adept at imparting his zeal and enthusiasm to others:

> He's a great salesman. But see, he has that vision, and he has that conviction, and he believes in himself. You can tell he believes it. And he's almost messianic in the sense, if you've ever listened to him, whether it's one on one, or to a group of a couple hundred people, you know, the time just flies by. He has that...it's a gift. You don't make those guys. They're born that way. Ted is one of them. He's one of the most natural, dynamic leaders that you'll ever meet.

Ted Greene was responsible for creating a great deal of the 'magic' that surrounded Hybritech in its early years. As president of the company, he continued to tell the story that he originally composed as a business plan to many different audiences in many different venues. He hyped the technology and the company at every opportunity, in order to attract money to an R&D operation that could never get enough. Greene became one of the prototypes of the biotech company chief executive and spokesperson whose activities investment banker Richard A. Bock described, in

the early days of the industry, as key in establishing, and maintaining or maximizing, company stock valuations:

> A company's chief spokesman – preferably the chief executive officer, but any high-ranking manager who can tell the company story in crisp, layman's terms – needs to become highly visible to the investment community. He or she should be on the road a lot, appearing frequently at seminars and luncheon meetings, and be readily available to the news media.[50]

This is exactly what Greene did. To all whom would listen, he talked about the commercial potential of hybridoma technology, the extraordinary properties of monoclonal antibodies, and Hybritech's scientific, marketing, and manufacturing capacities and capabilities. From the time he joined Hybritech early in 1979, through the company's IPO late in 1981, and its eventual sale to Eli Lilly in 1986, Greene tirelessly promoted the organization and its technologies. He addressed venture capitalists, academic collaborators, scientific and managerial recruits to the firm, government regulators, potential corporate partners, journalists, investment bankers, stock analysts and brokers, and private investors. Of all the duties that he took on as Hybritech's chief executive, telling stories and making projections that would capture hearts and minds was certainly the most important in terms of the company's success in business.

VP OF EVERYTHING

Greene started work as Hybritech's new president on March 1, 1979, and the company started immediately to change. The differences were subtle at first, and perhaps imperceptible to some, but Greene brought a commercial sense that the firm

---

[50] Richard A. Bock, "The Importance of Hype," Bio/Technology 4, October 1986: 865-867.

had lacked, as well as knowledge of how things are done in 'real' companies – those not staffed entirely by runaway academics. Howard Birndorf was perhaps the person affected most by Greene's arrival. Greene didn't relieve him of any duties. As VP of everything, Birndorf continued to be responsible on a day-to-day basis for all that was required to keep Hybritech's laboratories running as smoothly as possible. He would retain that operational responsibility for another year. The new president busied himself with marketing, finance, and strategic planning matters that Birndorf hadn't been working on. Birndorf didn't have experience in these areas, and, as hectic as things were at the company during this phase of its existence, he didn't have time to learn about them. So, having a new full-time chief executive in the building didn't ease Birndorf's workload, but it did mean that he now had a full-time boss. Brook Byers had been his mentor. His relationship with Greene was different. Greene describes how it got off on the wrong foot:

> When I arrived the first day, I walked into the place, and Howard goes to this cabinet and pulls out a bottle of Scotch, and says, 'Can I offer you a drink?' I said, 'Get rid of that, right now!' I decided that the only business experience that Howard had at that point was watching J.R. Ewing on Dallas on television. Howard had a lot to learn at that point.

Greene wasn't prepared for the frat house culture that the young academics had created at Hybritech, but he quickly figured out that he was a long way from Baxter and wisely tolerated a good deal of the looseness that characterized the organization. Hybritech lore came to include numerous cautionary tales about the hazards of drinking on the job in a biological laboratory regulated by the FDA. Walt Desmond recalls that in the early days of the company, alcohol was a standard office supply:

"We had TGIFs on Friday and it was traditional to stash a bunch of beer so you'd have some on Saturday. Ah, the innocent old days." Greene didn't want to dampen the researchers' enthusiasm and esprit de corps, but he also knew that the atmosphere would eventually have to change. He approved of, and encouraged and participated in, much of the socializing, but tried to curb excesses. He wasn't much of a disciplinarian, but Greene was a bit older than most at Hybritech. At thirty-five, he was chronologically one of the organization's senior members. The group knew that he was in charge, and began to look to him for signals concerning how they should conduct themselves and how the organization should function. Birndorf remembers that he chafed at every imposition of authority and professionalism, and that he didn't get along very well with Greene:

> I was never really good at taking orders. One of the problems that I've always had is that I resist authority. You know, part of it is I think I can do better, which may or may not be true, but I've always been tough to manage. Ted Greene and I were always butting heads. We never saw eye-to-eye. I didn't really like working for him. I tried to be a team player. On the other hand, I didn't personally like it. So you know, he came on in March of '79, and it was very busy, but he and I did butt heads about things.

The two had a lot of contact with each other on the job, and after Birndorf purchased a new car, a Honda Accord – "the first decent car I ever owned" – they carpooled on occasion. Birndorf recalls talking to Greene "about Japanese cars and stuff like that" on the way to work. Still, they never managed to sustain a friendship. Birndorf admits that he had a chip on his shoulder. He was harboring some resentment about the manner in which Kleiner Perkins had distributed ownership shares in the company. Royston's share was nearly three times larger than his, and

Birndorf had to fight Brook Byers to get as much as he did. And then, once the firm's research programs got underway, Birndorf felt like he was the one doing all of the dirty work. He was learning well a couple of lessons that he would later impart to others following in his footsteps. One was that venture capitalists are penurious in the extreme when it comes to sharing equity, they're real skinflints, and the second was that it's better to have a small piece of a big pie than a big piece of a small pie, or no piece at all. "That's one of the clichés that's been used over the years," Birndorf remarks, "but it's true." At the time, however, it was little consolation to him. To add insult to injury, Royston was given a seat on the board of directors, but Birndorf wasn't invited. "That was something I was a little perturbed about," he says.

From Birndorf's point of view, things didn't get any better when Greene came along. Hybritech did very well. The company expanded rapidly, so, in 1980, Greene began hiring experienced managers from the diagnostics and pharmaceuticals industries to take over various parts of the operation, parts that Birndorf had been running. Birndorf didn't question the wisdom or the necessity of these moves. He knew that as the company progressed, he was moving further beyond the range of his useful experience. He was distressed, nevertheless, as his responsibilities were reduced. He felt himself being pushed gradually away from the nerve center of the firm that he had founded: "First, I was VP of everything, then he [Greene] would hire R&D, and then I was VP of everything except R&D, and then he'd hire finance, and then I was VP of everything but finance and R&D, and then operations, so on." Part of Birndorf's concern had to do with the control that he was being forced to surrender, but another, perhaps larger part had to do with his compensation: "I started at twenty

thousand dollars, and then he [Greene] would bring these guys on at sixty, seventy, eighty, ninety thousand dollars, but I'd never catch up. I'd get these little raises and I was real resentful that I was doing the same work as everybody, but I wasn't getting paid. So I had a lot of problems with him about that, about my pay. I was real money conscious."

Birndorf's management style in the early days of the company also got him into some trouble with Greene and other executives who were brought in to direct traffic. Before Hybritech, Birndorf had never really supervised people. At Stanford and UCSD, he had been positioned on the bottom institutional rungs, below all but students assisting in the labs in work/study programs. He hadn't before directed people who were working full-time for a living, and who perhaps had spouses, children, and mortgages to worry about, as well as obligations to Hybritech. To ensure that the company became successful, Birndorf had begun driving himself relentlessly in a way he never had before, and he developed a tendency to push others in the same manner. He was impatient, and he had a penchant for yelling and screaming when things didn't work out the way he wanted. He had trouble accepting that events don't always unfold according to plan, and that ineptitude is an inescapable fact of life in human organizations. Birndorf was inclined to view accidents and errors as personal affronts.

His antics usually elicited stronger negative reactions from his superiors than from his subordinates. Birndorf barked, but generally refrained from biting. Once those below him in the organization became accustomed to his blustering, and learned that it was acceptable to yell back at him, his irascibility made him the target of

affectionate practical jokes. His assistant once ordered personalized memo pads that read 'From the dorf of Howard Birndesk.' Birndorf used the pads for a month before noticing.[51] Greene and the big bosses worried, however, that Birndorf was intolerant, that his outbursts were disrespectful toward employees, and that his volatility would create bad feelings and damage morale. Birndorf was encouraged to recognize, he says, "that the employees have a say in what goes on, that everything isn't an absolute, that you've got to govern your temper, and you can't just rush out and rant and rave about every little thing."[52] He acknowledges his shortcomings as a manager, and recognizes that he is better placed in different roles:

> I'm demanding, I don't suffer fools lightly, I'm abrupt, people say that I wear my heart on my sleeve in the sense that they always know where they stand, when I'm happy or not happy. I don't consider myself a great manager of people. In fact, those kinds of things, really, I hate having to deal with somebody's who's unhappy about something. What I really like is the action. You know, going places, doing things, getting things done, accomplishing something.

Eventually, Birndorf found a place at Hybritech that suited his particular talents and disposition. When the last of the vice-presidencies had been assigned, he was left with corporate development – the licensing and acquisition of technologies and materials (antigens, for example) from universities and other research organizations, and the formation of joint ventures and corporate partnerships with other commercial entities. Once word of hybridoma technology began to circulate in the diagnostics and pharmaceutical industries – and Greene, by all accounts did a superb job of publicizing and promoting monoclonal antibodies by issuing press

---

[51] Fjermedal, Magic Bullets, p. 123.

[52] Fjermedal, Magic Bullets, p. 131.

releases, talking to journalists and stock analysts, networking at trade association meetings, and so on – the company was inundated with calls from companies that wanted desperately to gain access to the revolutionary technology they had heard so much about. It fell to Birndorf to field them, to find out what exactly what the callers wanted, and to discover what Hybritech might be able to receive from them by way of trade. He was, in addition, expected to establish contact with organizations possessing scientific or technical resources (information, materials, personnel) that Hybritech lacked, expertise or capabilities in areas like marketing or manufacturing that Hybritech hadn't yet developed, or other complementary assets that could perhaps serve as the basis for a mutually beneficial alliance with the start-up.

The position was one in which Birndorf's determination and doggedness were virtues. They enabled him to excel. Larry Respess, Hybritech's chief counsel, worked closely with Birndorf and other members of the firm's upper management team in analyzing the financial and strategic implications of proposed deals, examining relevant legal issues, and negotiating and structuring contractual agreements. Respess found Birndorf to be ideally suited for work at the front end of the process: "One of Howard's endearing qualities is that he's very persistent, and by having someone like that, who has a nose for these sorts of things, and also has the quality of being persistent, deals get done, and I think that's one of his really great talents." Birndorf earned the nickname 'cruise missile' for the directness and precision with which he pursued his appointed tasks. Brook Byers says, "Howard is the kind of guy that what you do is define a target for him and then launch. And you can go away, it's going to

get done. Ted and I would talk and say, 'Shall we put the cruise missle on this one?"[53] Respess adds, "Howard is a very bright guy, and gifted, and I think that corporate development was a slot that, in my view, Howard just naturally fit into. He's proven to be very effective at sniffing out technologies, and so forth." Birndorf agrees that the job was an appropriate one for him at the time: "You know water seeks its own level. I sort of found my niche in corporate development."

Corporate development activities were important for Hybritech, not only for the tangible benefits associated with particular deals, but because, in the biotech industry, corporate partnerships are means of establishing the credibility of companies and unproven technologies. Developing biomedical products, and especially pharmaceuticals, is an activity that requires enormous amounts of capital. Small biotech companies typically raise money, as Hybritech did, first from venture capitalists, and then, if the company can convince Wall Street that its plans are viable, from public markets. Respess explains that if you're running a biotech company, then even before an initial public offering:

> ...you need to constantly reinforce in the mind of the investment community that you're a winner, and that they should invest in your company at some appropriate time, depending on what their investment objectives are. One of the things that was always considered important back then, and to a lesser extent is still important today, is to get some collaborative arrangement with a corporate partner as a validation of your technology.

The logic is that major corporations wouldn't invest in or enter into joint ventures with small biotech companies if they didn't believe that the technology was

[53] Fjermedal, Magic Bullets, p. 102.

conceptually sound, even though it may not yet have born all of its fruit.[54] So, biotech companies tend to go through a series of these transactions, in order to gain access to capital and other resources, but also to build their images. Hybritech was no exception. Doing deals was a means of keeping the company in the news, and to stimulate interest in the company's stock, even before it was made available for public sale. Hybritech put out press releases that announced scientific breakthroughs, the accomplishment of development milestones, the closing of financing deals, and the formation of corporate partnerships, so investors could see that the company was making progress. Respess adds:

> I don't know that establishing marketplace identification was ever the primary reason for making a deal, but it was more often than not, more than a trivial reason. We didn't do, as far as I was concerned, bad business deals just to keep the company's name out there. There was always a legitimate business objective that was being pursued, but it was always a necessity to do that. I think every company would have liked to have been able to raise all the money it needed to develop all of its technology and keep all the proceeds for itself, but that's just unrealistic.

So, corporate development was important for Hybritech, and for the first few years of its history, the firm was very active in exploring possible transactions and alliances. The company was widely regarded as one of the industry leaders in monoclonal antibody research and development. Only Centocor, founded in Philadelphia in 1979 by Hilary Koprowski of the Wistar Institute, and Genetic Systems, a Seattle firm established in 1980 by Bob Nowinski, a microbiologist working with monoclonals at the University of Washington and the Fred Hutchinson

---

[54] See Sean Nicholson, Patricia M. Danzon, and Jeffrey McCullough, "Biotech-Pharmaceutical Alliances as a Signal of Asset and Firm Quality," NBER Working Paper #9007, National Bureau of Economic Research, Cambridge, MA, 2002.

Cancer Research Center, could be mentioned in the same breath.[55] Hybritech was well ahead of both technologically and commercially, if not scientifically. It had quickly garnered a special reputation among biotech companies because it was the first, in 1981, to put diagnostic products on the market. Because Hybritech was running ahead of the pack, Birndorf was constantly entertaining offers, and his counterparts in big companies would return his phone calls and listen seriously when Hybritech was the party making the overtures. While he was vice-president of corporate development, Hybritech secured distribution, marketing, or cooperative research and development partnerships with dozens of groups, including major deals with American Cyanamid, Baker Instruments, Baxter Travenol, and Johnson & Johnson in the United States, Boehringer Mannheim and the government of the Walloon region of Belgium in Europe, and with Teijin, Mitsubishi, and Toyo Soda in Japan. Birndorf enjoyed being involved in the deals, and his position provided an added benefit – his assignments often got him out of San Diego for extended periods, and away from possible clashes with Ted Greene and other members of Hybritech's upper management team:

> In 1981, I traveled thirty weeks out of the year. I started going all over the world, and this was great for me. I had never been to Europe. I had never been to Japan, and all of a sudden, I'm off on these trips. I had one six week trip to Europe. The first time I went to Europe, I was

[55] Nowinski and Hubert Shoemaker, Koprowski's business partner, both visited Hybritech before starting their own monoclonal companies. Nowinski traveled to San Diego to see if Hybritech wanted to license antibodies against viruses and bacteria that he had cloned, and Shoemaker, who worked for Corning at the time, arranged a meeting on the pretext that Corning was interested in negotiating a partnership. After dismissing Ted Greene's monoclonal antibody idea late in 1978, the Syva diagnostics division of Syntex apparently realized its mistake, and, afraid that it would be left behind technologically, began courting Nowinski and Genetic Systems. A marketing deal was inked in 1981. According to Robert Teitelman's analysis of the bargain, Genetic Systems essentially gave away its diagnostic business to Syva in exchange for a moderate stream of revenues that would help fund the biotech's development of monoclonal antibody-based therapeutics. See Robert Teitelman, Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology, New York: Basic Books, 1989; ch. 8.

> there for weeks, and I was alone. It was really cool. You know, in time, the travel becomes much less attractive, but for me, this was, 'Wow!' It was the coolest thing.

Birndorf's job also included organizing the firm's scientific advisory board (SAB), its roster of external consultants. He established and formalized connections with a number of prominent bioscientists around the world. Ivor Royston was a member. So was Norm Klinman, whose 'splenic fragment' technique Royston used to make monoclonal antibodies before the invention of hybridoma technology. Antibody chemist Al Nisonoff, Gary David's mentor and Ph.D. advisor at Illinois was on the board, too, along with Bill Dryer, the Cal Tech biologist from whom Ted Greene first heard about hybridoma technology. In Greene's estimation, Dryer was "a brilliant guy." "We used to refer to him as Buck Rodgers," says Greene. "He was kind of like our visionary consultant." Among others recruited by Birndorf were renowned senior faculty members from nearby UCSD, including biologist Richard Dutton and chemists Martin Kamen and Nathan Kaplan, and several thought leaders in Royston's field of cancer immunotherapy – Joseph Bertino at Yale University, Clive R. Taylor at the University of Southern California, John Kersey at the University of Minnesota, and Karl Erik Hellström and Ingegerd Hellström at the Fred Hutchinson Cancer Research Center in Seattle. High profile hybridoma expert David Secher, an associate of César Milstein's at Cambridge, was brought on as well.

The consultants agreed to attend semi-annual meetings for $500 per day, plus travel expenses. The prospectus for Hybritech's initial public offering of stock in 1981 states that "the Company's purpose in these meetings will be to establish and revise Hybritech's priorities," which was certainly true, and SAB members did make

valuable contributions to Hybritech's research and development efforts. Claude Meares, for example, a chemist at the University of California, Davis, was on the SAB because of his involvement, beginning in 1981, in clinical trials of the company's in vivo cancer diagnostic system. Hybritech scientists had selected a chelation chemistry invented by Meares as a method of tagging antibodies with radioisotopes. Meares was asked to consult on the project and subsequently received an invitation to join the SAB. But just as important as the substantive scientific input received from the board was the glory reflected on the company. In most instances, the members were selected, at least in part, for the marquee value of their names. Affiliations with scientific luminaries signaled that Hybritech was a top-flight technical operation, poised on the cutting edge of scientific research in fields relevant to its development projects. Composing the SAB was an exercise in creating and crafting a corporate image. For Birndorf, organizing the board meetings was an excuse to have some fun, too. Of the first gathering held at the La Costa resort a few miles north of San Diego, he says, "Brook came, and our scientists were there, and we had a two day meeting. We had a banquet and it was just a blast. We told jokes. I got up and told a joke. It was just a lot of fun."

Birndorf never managed to become comfortable with his status or his salary in the company that he co-founded, and he eventually left in 1984 to take advantage of other opportunities: "I was disenchanted with my role," he says. I wanted to have a more active say in things." But being involved with Hybritech was a tempering experience for him. He was around from the beginning to watch the organization take shape and become successful. He performed many different tasks for the company,

and learned about all facets of the operation. He soaked up a lot of practical entrepreneurial know-how. By the time he was finished at the firm, he understood what start-ups require in order to prosper. Making good use of what he learned, and taking advantage of the extensive contacts that he established during his time at Hybritech, Birndorf went on to start six more biotech companies in San Diego in less than twenty years. Brook Byers and Kleiner Perkins were involved in all of them. In 1999, Byers remarked that his work with Birndorf at Hybritech "began a partnership between Howard and myself that has lasted for twenty-one years so far, and seven companies."[56]

Taking leave of Hybritech was difficult for Birndorf. He calls it "the toughest thing I've ever had to do in my corporate life." Hybritech was a special place – and not just for Birndorf. Many others recognized it, too. "Part of it," Birndorf says, "was that we were new. We were the first biotech company in San Diego, really." But it was more than just novelty. Hybritech was also original. It was different in kind. It was a place where Gary David, Russ Curry, Joanne Martinis, and the rest of the researchers could work on interesting technical problems unhindered by academic politics, disciplinary boundaries, and the ponderous bureaucratic machinery that governs the disbursement of funds in the sciences. For a time, Hybritech was a commercial enterprise that afforded scientists a remarkable degree of freedom in their work. For Tom Perkins and Ted Greene (and others at the business end of the operation), Hybritech was special because it represented an entrepreneurial

[56] Cynthia Robbins-Roth, From Alchemy to IPO: The Business of BiotechnologyFrom Alchemy to IPO: The Business of Biotechnology, Cambridge, MA: Perseus Publishing, 2000; p. 51.

opportunity in the pharmaceutical industry. The pharmaceutical business was one in which the obstacles confronting new entrants had, before the invention of recombinant DNA and hybridoma technology, grown to insurmountable proportions. Hybritech represented a new and unique chance to build a pharmaceutical company from the ground up. It was an opportunity of a kind that simply hadn't existed before new biotechnologies had been invented and transferred from academic laboratories.

For Birndorf, Hybritech was special because it was his. It was a place where, first of all, he could have a decent job and make some money (far more than he ever imagined, as it turned out). It was also a project to which he could devote all of his energies without reservation. It was a place where it made sense to him to work hard and cultivate ambitions. It was a place to have fun, and, as the company evolved, it became a place where he could learn – about entrepreneurship, but also about himself. Finally, Birndorf notes, with pride, that although Hybritech was a new kind of organization, it worked: "It was a rare mix of people that all clicked pretty well together. The lower level people, the mid-level people, and the upper level people all started clicking, and there was this real sense of urgency there, there was a collective sense of us against the world there. It was really quite a magical place." Despite himself, perhaps, Birndorf was largely responsible for the collective spirit of the place. He exemplified it. He poured himself into the company. Joanne Martinis comments:

> People say Howards's got all this stock and all this money and what did he do to deserve it? He busted his ass. He made the company work. He didn't do experiments, but it doesn't matter. Howard did something I couldn't have done. He physically kept us running – by talking to people, by getting what we needed. When we needed this or we needed that, when we had trouble, when we needed more space and La Jolla Cancer said we aren't giving you any more, Howard got us more.

> When equipment didn't work and we didn't have any money and we needed a cheap gamma counter or a cheap freezer, Howard found us one. He just did all of those things, and that made us work. Howard was in the right place at the right time, but he didn't flunk out. Howard got us to where we are.[57]

Brook Byers agrees. As the company evolved, Birndorf became increasingly marginalized within it. Like Royston, his visibility in the firm, and his influence on the company's day-to-day activities eventually waned. As others moved in to take control of the operation, the co-founders found themselves shunted aside. But Byers believes that Birndorf deserves much of the credit for Hybritech's success, especially early on, when just he and a handful of scientists and technicians were putting the place together, beaker by beaker, so to speak. Byers maintains that Birndorf played an important role in creating the unique entrepreneurial spirit that animated the firm. He saw that Birndorf's drive and ambition were contagious: "I think Howard's greatest contribution was his sense of urgency."[58]

---

[57] Fjermedal, Magic Bullets, p. 132.

[58] Fjermedal, Magic Bullets, p. 102.

IX. INDUSTRIAL DISCIPLINE

A prudent man profits from personal experience, a wise one from the experience of others.

Joseph Collins

CHAMPANGE AND LIQUID NITROGEN

Through the first half of 1979, Hybritech's scientists learned a great deal about using hybridoma technology and making monoclonal antibodies. The next step, then, for the company, involved generating revenues with the technological know-how that its scientific teams were accumulating. Ted Greene recalls the circumstance of the firm at that point in time: "Monoclonal antibodies was a sexy, neat scientific idea, but customers don't pay money for new, sexy scientific ideas. We had to come up with a product." It wasn't enough just to be able to fuse cells and clone hybridized B-lymphocytes. By 1979, numerous academic laboratories were reporting the production of monoclonal antibodies. None of these immunoglobulins had commercial value, however. Perhaps a small percentage of them could have been useful for medical or research purposes beyond the particularized ends of the laboratories that created them (almost certainly, most would not have been, for various reasons – low affinities or cross-reactivity, for example), but academic labs simply weren't in the antibody-peddling business. Their antibodies never made it to markets to be priced. In any case, in order to make money from monoclonal antibodies, manufacturers had to know how to make good ones, and good ones for specific purposes. They had to know what to do with the antibodies. In this respect,

Hybritech's head start in the commercialization of hybridoma technology was sizable. The company was well ahead of its competition.

Successfully culturing hybridomas was just a preliminary step toward the company's business objectives. To establish cultures, the firm's cell biologists performed fusions and 'plated out' the resulting hybrid cells – they deposited the hybridomas into the receptacles of ninety-six well microtiter plates. Some would then begin secreting antibodies into the supernatant filling the wells. When this occurred, Gary David and his assistants in immunochemistry went to work characterizing the globulins and selecting the best among them according to their abilities to bind to antigens. Generally, the best in commercial terms were those with high specificities and affinities, those that unerringly targeted antigens of interest to the exclusion of others, and that, having accomplished this, fit snugly and securely to specific determinants or epitopes – binding sites – on antigenic molecules.[1] Greene had promised Hybritech's board of directors that the company would see revenues from antibody sales before the end of year. When Hybritech received its second infusion of venture capital in July on the strength of his business plan, the company had the resources it needed in order to move ahead into the marketplace. Greene communicated to all in the company that it was necessary to push toward this goal without delay. According to Gary David, when Greene came on board as the

[1] In addition to affinity, avidity (i.e., 'functional' affinity), and lack of cross-reactivity, other important antibody characteristics with respect to immunoassay performance include pH range of immunoreactivity and non-specific binding properties under certain pre-defined conditions. See E. Dale Sevier, "Monoclonal Antibodies: Expanded Potential for Labeled Antibody Ligand Assays," American Journal of Medical Technology 1982, 48, 8: 651-653.

company's president, the tenor of the firm's activities, even in the labs, began subtly to shift:

> He certainly provided a better focus on business goals, and he certainly took over a very important aspect of the work, and that was interfacing with the outside community, and starting to collect collaborators, and ultimately, customers. He provided that, and I suppose, in a way, it became a little less academic, and little bit more commercially oriented. He helped to drive us to getting our first products out by the end of '79.

Greene organized the weekly technical strategy meetings that Ivor Royston attended and recorded, and he began teaching the academics how to organize industrial product development efforts. Walt Desmond remembers that Greene took on the responsibility of coordinating and directing the company's various technical endeavors, and that the scientists were pleased to let him do it: "We sort of left it up to him. We'd show up and be asked, 'How are all these projects going?' We'd go through all the antibody projects, and we were, I distinctly remember, introduced to words like milestones."[2]

Researchers were the first group of customers that the company intended to supply with antibodies. For months, Hybritech's scientists had already been trading antibodies with local colleagues and other professional contacts, in exchange for antigens and information. By the end of 1979, they were ready to start selling them. They prepared to take orders from academic institutions, clinical laboratories, and industrial research organizations. They knew what other researchers required – they

[2] In the provision of venture capital, the achievement of pre-established performance milestones often stands as a condition of continued funding for a high-tech start-up. In some cases, the attainment of technical, financial, or organizational goals may, by contractual agreement, trigger disbursements automatically. See Paul A. Gompers and Josh Lerner, The Money of Invention: How Venture Capital Creates New Wealth, Boston, MA: Harvard Business School Press, 2001, pp. 53-55.

didn't need to conduct marketing studies in order to understand this particular market. The idea was to take the best of the antibodies developed by the firm, bottle them and sell them by the milligram to others with interests in learning about particular antigens or what could be done with monoclonals. The first antibodies to be sold were the anti-hepatitis globulins that the company had been developing. Hybritech's scientists had conducted a good deal of research on monoclonals against various viral subtypes.[3] They had characterized the antibodies in detail. They were able to explain exactly how these molecules would aid scientists and clinicians working with the hepatitis virus (and how they would not, if improperly employed). After a full year of R&D using hybridoma technology, the company could finally advertise a useful biological product. In December, right on schedule, Hybritech was poised to become the first commercial source of monoclonal antibodies in the United States.

The company didn't have a manufacturing operation in place, and no manufacturing personnel, so everybody employed by the firm – Ted Greene, Howard Birndorf, and all of the scientists and technicians – helped out with packaging the first products. They took bits of frozen antibody serum, weighed them out on scales, and placed them in V-shaped vials, which were then capped, labeled, boxed, and shipped. Joanne Martinis remembers: "All of the scientists were sitting down in this grungy basement working at a table with a vat of liquid nitrogen as we hand-filled the vials."[4] Birndorf was in charge of printing out the labels. "I spelled hepatitis wrong," he

---

[3] G.S. David, W. Present, J. Martinis, R. Wang, R. Bartholomew, W. Desmond, and E.D. Sevier, "Monoclonal antibodies in the detection of hepatitis infection," Medical Laboratory Sciences 38, 1981: 341-348.

[4] Grant Fjermedal, Magic Bullets, New York: Macmillan, 1984; p. 130.

recalls. The labels didn't look quite right to Ted Greene, so a dictionary was consulted. Birndorf has kept some of the labels as mementos. The first sales were important, symbolically far more than monetarily, for almost everybody involved with Hybritech. To the employees, they represented success, a reason for continued optimism, and a cause for celebration. "Actually," Gary David says, "our first products were our New Year's Eve party. We were vialing them on New Year's Eve. I remember champagne and liquid nitrogen, which is an interesting combination."

As Hybritech's scientists pondered methods of scaling up their primitive manufacturing operation, they quickly realized that none among them had any experience in the area. They saw that they didn't really know what they were doing, and that the company could probably avoid many mistakes by hiring someone with expertise. So, in January 1980, Hybritech brought on board its first production supervisor, Jeanne Dunham. Dunham was originally from New Jersey. She had gotten married and given birth to two children shortly after graduating from high school. Later, at the age of twenty-eight, she returned to school for more education. In 1974, having earned an associate's degree at Rutgers University, she went to work for the Behring Diagnostics division of Hoechst AG in Somerville, New Jersey. While at Behring, she continued on at Rutgers, taking night classes after work in order to complete the requirements for a bachelor's degree in chemistry. When she was just six credits short of this goal, Behring purchased Calbiochem, a successful chemical reagent manufacturer that had been founded in San Diego in 1952.[5] Dunham's bosses transferred her to the new acquisition in order to build out laboratories in an expansion

project. (Dunham eventually completed her chemistry degree in 1980, by taking classes at UCSD. She then went on to San Diego State University for a master's degree in operations management, which she received in 1984).

Dunham arrived in San Diego to find Calbiochem in turmoil. The sale of the company and the introduction of a new executive regime had disrupted the firm's established order. Dunham says, "They had the old group from Calbiochem, and the new group from Behring, and they were trying to mesh, and it just wasn't working." Late in 1979, after little more than a year in this environment, she became dissatisfied with her status at the company: "There was a promotion of one of the people in the organization that was my equal, and I wanted that promotion." She was angered by the snub, and complained to a friend she had made at the company. The friend was Bob Wang – Gary David's former confederate at Scripps. Dunham recalls, "I said to Bob, 'I'm not happy. I'm leaving.'" Wang directed her to Hybritech. The timing was perfect. Dunham suited the start-up firm's pressing needs. She knew about biochemical manufacturing operations, and she was young – she was willing to work relatively cheaply. She filled out an application provided by Wang, interviewed with Howard Birndorf, and was hired immediately. As Dunham sees it, she was brought in because:

> I had just come from New Jersey and set up four new laboratories at Calbiochem from scratch. I hired all of the people, set up all of the procedures, got all of the equipment operating, and made product while that was going on. So, they knew that I could do things, make things happen quickly, and get that all done. So, I think that's the main reason Howard hired me.

---

[5] Calbiochem is today an affiliate of EMD Biosciences/Merck KGaA, of Darmstadt, Germany.

Dunham began piecing together a manufacturing process in one of three temporary house trailers that Hybritech had parked outside the La Jolla Cancer Research Foundation. In its first year, the firm had outgrown the laboratory space it had leased from the Foundation. Birndorf had asked for more room in the building, but the Foundation had none to spare. His request was denied. He then attempted to bring trailers onto the Foundation property, but the city's zoning regulations prohibited it. Birndorf persisted, the city eventually relented, and the company obtained permits for its temporary structures. Hybritech then had a little room in which to expand its operations. Dunham was on her own in one of the trailers, the only person in the firm with a background in manufacturing. She was familiar with making biochemical reagents, but doing it with hybridomas and doing it with academic scientists presented her with a set of problems that she had never seen before. She recalls that "the Hybritech thing was a whole new area to get into, dealing with the research people."

Dunham's first assistant came from within the firm: "They [Ted Greene and Howard Birndorf] suggested that perhaps I bring somebody from R&D into operations because they would know their way around the facility." Greene and Birndorf recommended Gary Jones. Jones had been looking after Hybritech's vivarium in the basement of the Foundation, tending to about fifty mice. Although he later became involved in the implementation of sophisticated production techniques at Hybritech, manufacturing processes at that time were foreign to him, even the basic system that Dunham initially designed. "Gary was not your typical operations person," Dunham says, "so I suffered through that for a couple of years." She hired two additional

helpers, Jim Neal and Randy Lane: "They were the hands-on people doing the daily activities. They were fresh out of school." Manufacturing at Hybritech was a novel experience for all involved. The work was full of uncertainties and surprises, the budget was meager, and the circumstances were unfamiliar. Fortunately, Dunham found the environment stimulating: "I'm a Type A, maybe Triple A, kind of person. I like challenges. It was definitely a challenge." She adds:

> Hybritech was fun. I wouldn't have traded it for anything. I can't honestly say I got my training there. I probably learned more from there about what not to do than what to do. I really think my training and the drive to do things correctly, to do them right, and to do them high quality, came from Behring Diagnostics rather than Hybritech. Behring was into high quality, and that was never compromised.

Hybritech was a beneficiary of the learning that Dunham had done at Behring and Calbiochem. She was the first new hire to bring an industrial background to the company. Many others like her would soon follow to make substantial contributions to the firm. Ted Greene was making a concerted effort to the change the culture of the place. He did it by populating Hybritech with business people. Greene's recruits remade Hybritech in the likeness of a more conventional industrial operation and, with remarkable speed, transformed it into a commercial force. Setting up a manufacturing process at Hybritech was an adventure, but Dunham turned her trailer into a workable production facility. She and her team began to prepare, package, and ship Hybritech's monoclonal antibodies with some semblance of efficiency. The firm's cell biologists and immunochemists continued to experiment with an expanding range of antigens, the company's product line became increasingly diversified, and Dunham worked to

ensure that the new antibodies made it out the door and into the hands of the firm's customers.[6]

At that point, Hybritech had realized the plans envisioned by Royston, Birndorf, David, and Greene when they first learned of hybridoma technology. The firm had become the kind of commodity antibody business that each of them, independently, had imagined. All enjoyed a sense of satisfaction, accomplishment, and vindication with the success of their common project, and the staff was enthusiastic about the company's future prospects. The venture capitalists did not share in much of the excitement, however. As far as they were concerned, the company's potential had little to do with its capacity to produce materials for research purposes. There wasn't enough money in it. Rather, the promise of the company had to do with its chances to develop immunoassays that would substitute monoclonal antibodies for polyclonal mixtures, and thereby significantly improve the performance of diagnostics tests sold in high volumes to clinical laboratories. As Brook Byers noted, announcements about the successful manufacture of monoclonal antibodies didn't impress anyone in the diagnostics industry: "That's like saying you've got silicon and you still have to make a semiconductor."[7] As a veteran of the diagnostics business, Ted Greene understood what had to be done.

---

[6] Eventually, the company sold monoclonal antibodies against a variety of enzymes, hormones, blood proteins, cancer markers, and infectious agents, including alpha fetoprotein (AFP), alpha interferon, calcitonin, carcinomembryonic antigen (CEA), chlamydia, chorionic gonaotropin (HCG), creatine kinase (CK-BB and CK-MM), endotoxin, factor VIII, factor IX, growth hormone (HGH), hepatitis (four subtypes), antibodies (IgD, IgE, IgG), leutenizing hormone (LH), prolactin, prostatic acid phosphatase (PAP), prostate specific antigen (PSA), trichomonas, and thyroid stimulating hormone (TSH). See Hybritech, Inc., Stock offering prospectus, November 10, 1982.

[7] Fjermedal, Magic Bullets, p. 100.

THE TANDEM™ ASSAY

After Hybritech's first research antibodies had shipped, the company's next objective was to design a diagnostic product and push it out the door. The goal was simultaneously scientific, technological, and commercial – challenges and problems of each sort would have to be overcome or managed if Hybritech was to achieve its ends. Initially, Gary David and Ted Greene did most of the planning. The pair had begun putting their heads together as soon as Greene arrived at the company in March 1979, to design an immunoassay that would take advantage of the special properties of monoclonal antibodies, and could be adapted for incorporation into a diagnostic kit. Greene remembers: "I presented Gary with this problem of 'We've got to come up with a product,' and over a period of time, the two of us worked out this concept that we ended up calling the TANDEM assay."[8] The TANDEM assay became the basis for most of the diagnostic kits that Hybritech would manufacture over the next several years.

The TANDEM format was so-called because it was a 'two-site', or 'sandwich' IRMA (immunoradiometric assay) that incorporated two different monoclonal antibodies. As David and Greene conceptualized it, one antibody was to be attached to a solid phase. It would be selected for its ability to bind a specific antigenic determinant on the immunogen to be detected and measured; the other antibody would be soluble, labeled with a radioisotope (or an enzyme or fluorogenic compound) and targeted against a different binding site on the immunogenic molecule. Together, the

[8] Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies," U.S. Patent 4,376,110; filed August 4, 1980; issued March 8, 1983.

two antibodies would 'sandwich' the antigen. Immobilized on the solid phase support, the resulting antibody:antigen:labeled-antibody complex would then be washed and read by a gamma counter (or, if the labels were enzymatic or fluorescent, by colorimeters, fluorometers, spectrophotometers, or visual inspection).

When David and Greene began discussing possible formats, they agreed immediately that they needed to develop a solid phase 'IRMA' of some sort (or, for certain purposes, equivalents with different kinds of labels, ELISAs, for example – enzyme-linked immunosorbent assays). David had devised the solid phase assay that Hybritech used to screen hybridomas, so he was familiar with the format, and practiced in its application. Further, David and Greene were both aware that, in the field of immunoassay technology (although not yet, at that point, in the market for clinical diagnostic tests), IRMAs had come to represent the 'state of the art.'[9] Immunometric procedures offered definite advantages in comparison to the original competitive radioimmunoassays invented by Yalow and Berson.[10] First, in immunometric tests, antibodies are labeled, while in radioimmunoassays, antigens are labeled. Chemists prefer antibodies because they are typically easier to work with. They are designed by nature to bind to things. Antigens, by contrast, are often

---

[9] Roger Ekins notes that the only immunometric test to achieve substantial commercial success in the 1970s was Abbott's a 'two-step' IRMA for hepatitis B. The kit became popular, Ekin asserts, because "the unusually large size of the antigen molecule... caused difficulties in distinguishing between free and antibody-bound antigen moieties in a conventional RIA." A few ELISAs gained market share, too, not necessarily because they were more sensitive or accurate than competitors, but rather because nobody likes being exposed to radioactivity if it can be avoided, and enzyme-based tests spare labs much of the bother associated with hazardous waste disposal. See Roger P. Ekins, "Ligand Assays: From Electrophoresis to Miniaturized Microarrays," Clinical Chemistry 1998, 44:2015-2030.

[10] See Chapter Six, pp. 47-55, for a comparison of radioimmunoassay and immunoradiometric assay technologies.

difficult to tag. Some resist being labeled with isotopes (or enzymes, fluorogens, or chemiluminescent compounds), and some flatly refuse to cooperate. And even when obdurate antigens submit and accept their tags, they are far more likely than antibodies to change their minds and shed them subsequently. So, as reagents in diagnostic tests, labeled antibodies are more stable and reliable than labeled antigens.

Secondly, because immunometric tests employ reagents in excess, they feature an extended dynamic range, a greater signal-to-noise ratio. For clinicians, this means tests with greater sensitivity. Immunometric assays can detect and give accurate quantitative indications of antigens at very low concentrations. The reagent excess also makes immunometric tests faster. Because they rely on mass action, they reach equilibrium – the point after which the formation of antibody-antigen complexes in solution does not increase with additional time – sooner than do competitive assays. In competitive radioimmunoassays, limited amounts of antibody compete for binding sites on labeled and unlabeled antigen, both of which are present in limited quantities. Under these conditions, it takes the antibodies longer to swim through the solution and to find all of the available sites. The critical variable becomes the affinity of the antibody preparation, and even when this is high, the reaction is less efficient than one driven by mass action. Incubations in competitive radioimmunoassays usually take many hours or even days to reach equilibrium. In immunometric procedures (or those employing monoclonal antibodies, at least), the durations are reduced to periods that are often measured in minutes rather than hours – thirty, sixty, ninety, or one hundred

and twenty minutes.[11] Finally, in IRMA formats, recorded binding activity of labeled antibodies represents a direct measurement of the concentration of an analyte in solution. In radioimmunoassays, the proportion of bound labels to unbound labels serves as an indirect measure of the concentration of unlabeled free antigen in a sample. Because every measurement introduces error, the single, direct approach of the immunometric test is preferable to the dual measurements of radioimmunoassays.[12]

Immunometric designs are generally faster and simpler than relatively cumbersome radioimmunoassays. Yet, before the invention of hybridoma technology, competitive RIAs retained one big advantage over IRMAs – they require fewer antibodies.[13] The excess reagent design of the immunometric format necessitates the use of antibodies at high volumes. This is a problem in labeled antibody formats when polyclonal mixtures are employed. An accurate immunometric reading of an analyte present in a sample requires labeled antibodies that are specific for the target, but immunizations in animals elicit the production of antibodies exhibiting a wide range of specificities. In order to attenuate the natural variability and crossreactivity of

---

[11] Roger P. Ekins, "Ligand Assays: From Electrophoresis to Miniaturized Microarrays." See also Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies."

[12] According to Ekins: "In general, direct measurement of occupied sites represents the better strategy, generally yielding higher sensitivity. (Analogously, it is preferable to determine a 1-cm length by measuring it directly rather than subtracting measurements of two greater lengths, e.g., 1 m and 99 cm, each of which is subject to error)." See Roger P. Ekins, "Ligand Assays: From Electrophoresis to Miniaturized Microarrays."

[13] Standard radioimmunoassays are still preferred for certain purposes. 'Two-site' IRMAs are often inapplicable when small peptides, for example, are to be identified and measured. These molecules may be too small to display two remote antigenic determinants. For the detection of small peptides, RIAs remain the preferred tool. See Rebecca Krumm, "Radioimmunoassay: A Proven Performer in the BioLab," The Scientist 1994, 8, 10:17.

heterogeneous polyclonal sera in IRMA formats, it is necessary first to purify the antibodies. Antibodies that are specific for the immunogen must be separated from antibodies that are not. This is typically accomplished by solid phase adsorption in affinity chromatography. But this procedure is hard on antibody proteins, and the affinities of immunoglobulins that survive it are typically mediocre. Low affinity antibodies are generally not well adsorbed; many are washed out and lost. The highest affinity antibodies are often destroyed by elution (removal from the solid phase) or damaged by incomplete elution. Thus, the purification of polyclonal antibodies results in low yields of less than ideal reagents. Immunometric procedures feature some distinct advantages over conventional RIAs, but these advantages depend on the use of reagents in excess, and generating purified polyclonal antibodies in sufficient quantities is convoluted, difficult, and costly.

Even after purification, the crossreactivity of polyclonal anitbodies may still trigger false positives in IRMAs, just as in standard RIAs. The crossreactivity of polyclonals can be reduced by purification, but not eliminated. In addition, certain IRMA designs are rendered susceptible by polyclonal reagents to other kinds of problems. In 'reverse' assays, for example, the immunogen-containing sample is exposed first to labeled antibodies, and then, after that reaction has reached equilibrium, the solid phase carrying unlabeled antibodies is added. In 'simultaneous' procedures, the sample is exposed to labeled and unlabeled antibodies at the same time. In both of these formats, it is possible for soluble, labeled antibodies to form antigen-antibody complexes that interfere with the binding of antigen with insoluble antibodies on the solid phase. When this kind of 'steric' interference occurs,

unanchored complexes are washed away and not counted.[14] At low antigen concentrations, steric hindrance compromises the precision, accuracy, and detection sensitivity of immunometric assays. High antigen concentrations, by contrast, may produce what is known as the 'high dose hook effect.'[15] If, in a 'two-site' immunometric assay, the binding sites of antibodies are saturated to a significant degree by antigen, the resulting antigen:soluble antibody complexes will be prevented from stabilizing as sandwiches on the solid phase. Again, as in cases of steric hindrance, the complexes will be flushed during a washing step before being counted. The test will then give low, normal, or only slightly elevated readings, although the actual concentration of antigen in the sample is very high.

These problems are not a concern in 'forward' IRMAs. In 'forward' tests, the sample containing the immunogen to be identified and measured is exposed first to the insoluble, unlabeled, anchored antibody. Following incubation and a wash, antigen bound to the solid phase remains free to react with labeled antibodies, which are added subsequently. Forward assays, however, call for two incubations and two washes. Reverse and simultaneous assays eliminate one or more of these steps and are simpler

---

[14] The term 'steric' refers to the organization of atoms in space, to molecular configurations at the atomic level. Steric hindrance occurs when labeled antibodies take molecular parking spots that have been reserved, so to speak, in the context of an immunoassay, for insoluble antibodies, or, when antigenic determinants are situated in close proximity to each other on an immunogenic molecule, labeled antibodies park themselves in these spots in ways that block other antibodies from access to adjacent binding sites.

[15] The term 'high dose hook' refers to the shape of the curve that plots the strength of the signal produced by labeled antibodies captured in sandwiches on the-X axis in relation to antigen concentrations along the Y-axis. In a reagent excess, immunometric test employing monoclonal antibodies, the expectation, roughly, is a linear association with a positive slope of one. When the saturation effect occurs at high antigen concentrations, however, a hook appears at the end of the curve far out to the right above the Y-axis and dives precipitously, indicating a decrease in signal past the point of saturation.

to perform. Forward assays are relatively labor intensive and time-consuming, but in the late 1970s and early 1980s, they were preferred in clinical laboratories – to the extent that IRMAs had penetrated the market – because of their greater reliability. David and Greene recognized that monoclonal antibodies could remedy many of the flaws that had prevented IRMAs from attracting larger shares of diagnostic kit sales. They were aware that Abbott had invented and marketed a 'forward' immunometric assay for detecting the hepatitis B virus in serum with ^{125}I-labeled polyclonal antibodies.[16] This test represented the 'prior art' on which they intended to improve with monoclonals. They looked at it, and at other available immunoassay formats, and began searching for ways to make such tests faster, more sensitive, and more reliable.

Hybritech had made monoclonals against hepatitis, so David began experimenting with sandwich IRMAs using hepatitis antigen from a competitive radioimmunoassay kit marketed by Abbott. His laboratory notebook reported a failed attempt on May 27, 1979, in which no binding was detected, but recorded successes on August 3, 1979, with a sandwich assay that employed a single '068' monoclonal antibody to hepatitis (which worked, presumably, because of the size and heterogeneity of the antigen, and the crossreactivity of the antibody), and on September 21, 1979, with a reverse assay that utilized an immobilized '259' antibody and a radiolabeled '068' antibody.[17] David and Greene (and all of the others at

---

[16] Chung-Mei Ling, "Direct radioimmunoassay for antigens and their antibodies," U.S. Patent 3,867,517; filed December 21, 1971; issued February 18, 1975.

[17] Hybritech Incorporated v. Monoclonal Antibodies, Inc., Appeal No. 86-531, United States Court of Appeals for the Federal Circuit, September 19, 1986. The numbers indicate different clonal lines from the company's hybridoma library.

Hybritech who contributed to the project by preparing antigen, making and screening antibodies, constructing assay materials, and so on) kept working to refine the technique, to make it perform with the kind of reliability that clinical laboratories expect from commercially packaged immunoassay kits. On August 4, 1980, satisfied that this had been accomplished, David and Greene, and the company, filed for a patent on the process. The application described methods for conducting diagnostic IRMAs with monoclonal reagents. The authors summarized the value of the claimed invention in this way:

> ...one object of the present invention is to provide an improved process for the immunometric assay for antigenic substances.
>
> More specifically, an object of the present invention is to provide more rapid immunometric assay techniques.
>
> Another object of the present invention is to provide more sensitive immunometric assay techniques.
>
> Yet another object of the invention is to provide improved "simultaneous" and "reverse" immunometric assays.[18]

These advertised improvements derived mainly from the application of hybridoma technology to the prior art in immunoassay design. They depended, according to the inventors, principally on the skillful creation and screening of two distinct monoclonal antibodies displaying high affinity for target analytes.[19] These

---

[18] Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies."

[19] According to the patent, selected antibodies would have to exhibit affinities of at least 10^8, and, preferably, 10^9 liters/mole if the invention was to constitute a genuine improvement over prior art. See Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies." Affinity constant ratios are calculated with data from assays that determine equilibrium concentrations in solution of bound and free antigen at increasing concentrations of antigen in relation to fixed concentrations of antibody. For a discussion, see William E. Paul, Fundamental Immunology, 4th ed., Philadelphia, PA: Lippincott-Raven, 1999; p. 79.

antibodies would be carefully selected for characteristics matching the specific biochemical requirements of particular embodiments of the invention,[20] and would be directed against two distinct antigenic determinants sufficiently distant from one another to eliminate problems of steric interference. Previously, the high incidence of interference problems with the use of polyclonal reagents had seriously hampered the commercial viability of reverse and simultaneous assays. David and Greene believed that the application of hybridoma technology would enable Hybritech to take advantage of the sensitivity, speed, and simplicity of all immunometric assay designs, while simultaneously solving the problem of antibody supply and enabling the production of reagents less prone to crossreactivity, steric interference, and antibody saturation (the high dose hook effect). The '110 patent,' as it later came to be called in the course of litigation over its validity, staked out an expansive territory of technical practice and commercial opportunity. Claim 19 of the document was the broadest. An impressive combination of scientific and legal prose – a single, protracted and dense, but, in the end, grammatically incomplete sentence – claim 19 covered the incorporation of monoclonal antibodies into each of the three principal immunometric assay formats – forward, reverse, and simultaneous:

> In an immunometric assay to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance

[20] These would include, according to claims 3, 16, and 27 of the patent, immunometric assays to determine the presence or concentration of IgE, hepatitis A, hepatitis B, hepatitis Non A/Non B, alphafetoprotein, carcinoembryonic antigen, insulin, and human thyroid stimulating hormone, and in which, according to claims 8, 17, 28, labeled antibodies would be tagged with either a radioactive isotope, an enzyme, or a fluorogenic material. See Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies."

> in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, the improvement comprising employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.[21]

DODGING THE GORILLA

Although Ted Greene didn't conduct any experiments at the lab bench, he is listed as an inventor on the '110 patent,' along with Gary David. According to David, "Ted was one of the primary people involved in the discussions that led to that technology. He certainly contributed intellectually as much as the rest of us did." Greene maintains that the greater part of his role was persuading the scientists that a simultaneous assay could be made to work well with monoclonal antibodies. He pushed them to try it. In David's view, Greene was the genuine article, a real inventor, largely responsible for the patented idea and the reduction of the idea to practice, and deserving of the honorary title of 'scientist':

> Ted contributed an awful lot, and was really very much on our wavelength. Ted was somebody who was very excited about science and technology, and really, that excitement was awfully important in generating our excitement and maintaining our focus. He certainly stimulated ideas. He had lots of ideas. Ted is probably a lot closer to a scientist than an awful lot of so-called scientists that I've known.

From the beginning, Greene tried to nudge Hybritech in a commercial direction, but he fit in well with the academics, nonetheless. The company probably could not have hoped for a better person to serve as its first president. During the 1979-1980 period, Hybritech was almost exclusively research driven. It was basically an R&D operation that happened to be selling some of the byproducts of its scientific

[21] Gary S. David and Howard E. Greene, "Immunometric assays using monoclonal antibodies."

inquiries. The firm was fostering a new kind of environment for conducting scientific work. A naturally occurring, uncontrolled social experiment was taking place at Hybritech – the cultivation of a novel organizational culture, an academic/industrial hybrid. Cells were not the only things being hybridized in the company's laboratories. People were, too. Hybritech was a place where progress in science, technology, and commerce were indistinguishable. This was an ideal setting for Ted Greene. He had a business background, but he loved science and understood scientists. He was also energetic, congenial, and creative. Dick Schneider is an Orange County venture capitalist who, over the years, has been deeply involved, like Ted Greene, in the formation of the San Diego biotechnology industry.[22] Schneider recites from the local book on Hybritech's first full-time president:

> He's a one of a kind guy. He's about as challenging as you'll ever find anyone to deal with. He comes up with so many ideas, some of them are nuts, but they deserve attention. You've got to listen to them. They make sense in a funny sort of way. In his mind, they do. So, he's just a bundle of energy. He's constantly coming up with new things, and he's just a lot of fun to work with. People are really attracted to a guy like that. He's just a special case, I think. Just a special case.

Luckily for Greene, for Hybritech's scientists, and, in all likelihood, for the subsequent fortunes of the company, the impulse that animated Hybritech throughout its start-up phase, the impulse to make scientific discoveries and extend technological capabilities, did not conflict with the economic imperatives of doing business as a

[22] Schneider is also a Ph.D. chemist. When Hybritech was getting started, he was a chief scientist and manager at the Syva diagnostics division of Syntex, and, in 1980, had just been promoted. At that time, he was approached by Brook Byers and Ted Greene about taking the position of vice-president of R&D at Hybritech, but he declined; "I told them that I was perfectly happy at Syntex and Syva, that this was my whole life, that I really loved doing it, and who are you guys anyway? What kind of a crazy, wild ass idea is this?" Schneider may have been content at Syva, but he was nevertheless soon lured away by technical opportunities in biotechnology. None matched Hybritech's success, however. "One of the bigger mistakes of my life," he says now, "was not to take that one."

diagnostics manufacturer. The pursuit of science and the pursuit of profits were almost entirely complementary, if not identical, during this period. Most of Hybritech's scientists had joined the firm because the technical challenges were so appealing. The company was never short of puzzles and problems to solve, so most of the scientists were happy most of the time. It was easy for Ted Greene to let them remain that way, and because the science and the business were both moving ahead, he was happy, too. Gary David recognizes that, as the leader of a science-driven biotech start-up, Greene was in his element:

> He was a thinker. He enjoyed it. He loved science, and while his position, background, and training certainly made him oriented toward the dollar sign, it would have been interesting if it had ever come down to a question of 'Do we go after money, or do we go after science?' It would have been interesting to see the conflict that would have taken place in Ted. He was a lot of fun.

In addition to displaying his talent and enthusiasm for science, Greene demonstrated his business savvy, as well, as Hybritech took its first steps toward entrance into the diagnostics marketplace. From the time Ivor Royston first explained to Tom Perkins in the lounge at San Diego's Lindbergh Field that tests to detect the hepatitis virus in blood comprised the largest market in the medical diagnostics business, Hybritech had devoted most of its resources to working with hepatitis antigens and making monoclonal antibodies against them.[23] Now that the firm had shifted its focus to assay development, Hybritech's scientists were thinking about how to make improvements in

---

[23] See G.S. David, W. Present, J. Martinis, R. Wang, R. Batholomew, W. Desmond, and E.D. Sevier, "Monoclonal antibodies in the detection of hepatitis infection," Medical Laboratory Sciences 1981, 38: 341-348.

existing diagnostics kits for the virus that would appeal to potential customers in clinical laboratories and blood banks. Gary David recalls: "We were still locked onto the hepatitis surface antigen, and we were still trying to put together an assay that would be commercially viable." At this juncture, Ted Greene gave Hybritech's technical and commercial strategies an unexpected twist. Ivor Royston was still following the progress of the company on a day-to-day basis, attending the weekly technical strategy meetings on Fridays, and recording the minutes. He reports that, at one of these meetings, sometime in late 1979 or early 1980, Greene dropped a bombshell that caused everyone involved in the R&D effort to pause, redirect their thinking, and alter their plans of action:

> It was just natural to assume, 'OK, we're going to make hepatitis test kits and sell them,' because that was the number one test. But Ted Greene said, 'Nah, I don't like that idea. The worst mistake you could make in this business would be to go head to head with Abbott, which has the market share of hepatitis testing. Abbott will find some way of getting around you, getting antibodies of their own, and they'll just kill you. We shouldn't do that. We should work on another test that Abbott's not focused on.' And so, he, as the president of Hybritech, made the executive decision, supported by the board, I think, that we would not use those antibodies to develop a product, a test. We'd sell them, if anyone wanted to buy them in a bottle, but we wouldn't use them.

At the time, Abbott was the largest producer of radioimmunoassays in the world. Its RIA sales more than doubled those of its nearest competitor, Roche Diagnostics. Unlike the naïve academics who surrounded him, Greene appreciated and was wisely chary of Abbott's size, resources, and competitive ferocity. "We didn't want to take on the gorilla," he says. "Hepatitis was their number one profit-

maker, and anybody that tried to come into that business, they would crush.[24] Gary David reveals that the president's opinion on the matter soon became the common sense of the firm. What had occurred at first only to Ted Greene quickly became accepted by most within the company as a self-evident truth – inciting a fight with Abbott over hepatitis would be foolhardy: "It became obvious that it made no sense for us to go up against Abbot in a market that was totally dominated by one very large player. It made much more sense for us to jump into a niche market."

Hybritech's decision to back out of hepatitis was reinforced by the knowledge that regulatory approval of a blood test for the virus could not be obtained simply by meeting the requirements of a standard 510(k) notification to the Food and Drug Administration. The object of a 510(k) submission is to establish the fundamental equivalence of the performance of a new medical device with the performances of other devices of the same class already on the market. For an assay to detect hepatitis, a PMA, an application for pre-market approval, would have been required. The pre-market approval process would have entailed a costly clinical trial of the test, along with extensive validation studies and meticulous documentation of all materials and procedures involved in the manufacture of the kit. The company decided that it would instead select a different analyte and manufacture a kit for which a 510(k) notification

[24] Hybritech would eventually have several run-ins with Abbott, in the marketplace and in the courts, and the start-up instigated at least a couple of them for strategic purposes, but Greene was well aware of Abbott's history and notoriety in the diagnostics industry. "When the RIA business got started in the 1970s," he explains, "the guys at Abbott figured out that there were a number of small, independent companies that were basically making their living off of these tests, and investing money in development, so they just cut the price and drove everybody out of business on those assays, just drove them out of business. A guy in Boston, Jerry Goldstein, who had one of those companies, if you say the word Abbott in front of him, he'll just go, you know, 'Aaaggh!' So, they were ruthless. And, in fact, they have a reputation in this industry of being the bad guys."

would suffice. David says, "The blood banking system brought with it a host of regulatory issues that just didn't make sense to get into." The idea of developing a simultaneous IRMA for hepatitis was scrapped.

The company started searching for another project with which to introduce hybridoma technology to the diagnostics marketplace, though the move was disorienting and required Hybritech's R&D teams to downshift and surrender some of the momentum that they had generated. The firm had learned a lot about how to deal with the unique problems that the hepatitis virus poses for biochemists, immunologists, and medical researchers, but much of that know-how was now to be set aside. Ivor Royston describes the decision as an important one, not just in strategic terms, but also in terms of defining the relationship between science and business at Hybritech. Ted Greene was adept at straddling the line that separated the scientists and business people in the company, but the line was still there. It persisted because participants in the process recognized it – often by habit, but sometimes by choice. They worked purposefully to maintain the boundary whenever it became useful to identify persons by their histories, associations, and experiences, and that, naturally, was often. Reflecting periodically on 'science' and 'business,' and especially when critical issues were on the table, became an integral part of the firm's hybrid culture. Royston believes that abandoning the hepatitis project was a good move. It was a prudent choice in that particular situation because Abbott was scary and the scientists needed to recognize that, but also valuable because of the general policy implications – Greene's authoritative imposition of commercial horse sense set a precedent:

> In retrospect, when I think about that, it was the right decision, because Centocor eventually made hepatitis antibodies and they licensed them to Warner-Lambert, and Warner-Lambert tried to market them against Abbott, and they got killed. So, in retrospect, I think that was the correct decision, and it shows you the importance of bringing in sound business people who knew how to make the right business decisions, and not let the scientists try to run the company.

Kleiner Perkins, drawing on lessons that early West Coast venture capitalists had learned in the course of their dealings with engineers in Silicon Valley, had insisted from the very beginning that the entrepreneurial scientists would not have executive control of Hybritech. That was one of the conditions of the initial financing. Royston was allowed to participate on the board of directors, and Howard Birndorf was granted operational control on a day-to-day basis, but Tom Perkins, Brook Byers, and Ted Greene were calling the shots. Royston now believes that this was one of the keys to Hybritech's success. "I've seen too many companies go bad," he says, "because the scientists had too much influence. Scientists are really not necessarily the best business people, and what makes a successful company is the marriage of the science with the business world, scientists and business people working together." Of course, scientists and business people don't always work well together, and sometimes companies suffer for it. Today, after many years of viewing conflicts between scientists and businesspersons from executive suites, Howard Birndorf has defected fully from his former tribe. For him, 'the scientists' have become 'the other.' "There are always problems with the scientists," he complains. "Scientists are unrealistic when it comes to business. They don't understand it. They're not necessarily good at it. Some are, some aren't. It's like anything. It's difficult to explain to them,

sometimes, the economics." In this instance at Hybritech, however, the scientists were willing to let go of hepatitis and move on to the next challenge.

WHEN THE TIME CAME TO GET REALLY SERIOUS...

After Ted Greene issued his edict against hepatitis, there were deliberations at Hybritech about which analyte to pick as a target for a clinical diagnostic test kit. The company pretty quickly settled on IgE (immunoglobulin E), the class of antibody involved in human allergic reactions. IgE responses are normally protective – they mobilize the host's defenses against certain parasites, for example – but they can also be harmful. In instances of allergenic pathology, production of IgE is triggered by exposure to allergens, i.e., substances that are ordinarily innocuous and display no special toxicity or immunogenicity (several kinds of insect and reptile venom are exceptions), but which, in certain individuals, become antigenic and stimulate hypersensitive immune responses – allergic reactions. The immediate humoral response consists in the clonal activation of IgE producing lymphocytes. The cascading cellular response that follows is initiated by the binding of IgE to effector cells in tissues (mast cells) and circulating in the blood (e.g., basophils and eosinophils), which then release histamines. Ensuing cellular interactions produce acute and chronic inflammation, in varying degrees of severity.

Serum tests that detect levels of IgE can be used to diagnose allergies (or perhaps, in certain contexts, parasitic disease). Hybritech opted to develop an IgE kit because the firm had already manufactured anti-IgE monoclonals, and the market for allergy tests was large enough to make the effort worthwhile, but not so big that the introduction of a superior product would provoke the ire of industry giants. Abbott

and the Ortho Diagnostics division of Johnson & Johnson, the two largest companies in the field, were focused mainly on hematology, where the big money was.[25] They weren't players in allergy diagnostics. Further, Pharmacia had begun selling a solid-phase immunometric allergy test utilizing polyclonal antibodies. Given this, Hybritech expected to be able to file a 510(k) pre-market notification for their own IgE test, rather than a PMA, which would likely have made the costs of the project prohibitive. If the FDA reviewers agreed that the company's data demonstrated the equivalence of the monoclonal kit, then Hybritech would be able to market the product within ninety days of the filing.

Hybritech's subsequent push to manufacture a diagnostic product with monoclonal antibodies led to increasing organizational diversification within the firm – in addition to cell biology, immunochemistry, and manufacturing, the company began assembling a product development team. Among the first hires were Gary David's buddies from Scripps, Bob Wang and Dale Sevier. David started talking to both of them about Hybritech during the summer of 1979. He wanted them because they were friends, they were experts in immunoassay technologies, and they would be arriving with experience in commercial operations. Wang was back in San Diego, at Calbiochem, after leaving Scripps in 1975 to take an industrial job and to move back home for a time to the San Francisco Bay Area. Sevier had left Ralph Reisfeld's lab in 1976, to fill a research position at Bioscience Laboratories, a clinical reference business located in Van Nuys, California. Both were impressed with hybridoma

[25] According to an IMS (Intercontinental Marketing Service) survey, the total market for allergy tests in the U.S. during 1980 amounted to less than $5 million; sales of hematological tests surpassed $90 million.

technology, attracted by the idea of a start-up company, and eager to work with Gary David once more. Sevier returned to San Diego to join Hybritech in August 1979. Wang wanted first to honor a commitment to Calbiochem, and so waited until March 1980 to join the company. Together, Sevier and Wang comprised – informally – the first product development unit at the firm.

Ivor Royston recalls that, at some point late in 1979, Ted Greene announced that it was time to enlist the services of a development specialist at the vice-president level: "Ted said, 'You know, we really need to bring on a real experienced research and development director who knows how to make products.'" Greene had someone in mind – Tom Adams, his former colleague at Baxter, with whom he had developed a new process for making chemical reagents in 1976. Greene decided that he had to have Adams, who by this time had settled in Connecticut, in an enviable position as a vice-president of chemistry R&D at Technicon, one of the nation's premier manufacturers of instrumentation in the laboratory supply and clinical testing business. "Tom is one of the smartest product development people I know," Greene says, "probably the smartest. When the time came to really get serious at Hybritech about product development, the only man I wanted to lead our research was Tom Adams."

Tom Adams grew up in California in the 1950s and 1960s. He was interested in science as far back as he can remember. As a kid, he became involved in what he calls "the usual stuff – building rockets and that kind of stuff." After graduating from high school, he enrolled at Chico State University and majored in chemistry. He spent two summers during his college years working as an NIH undergraduate trainee in the biochemistry department at the University of California at Davis. "That was a good

experience, working with the graduate students and the various faculty members over there," Adams says, "and I decided that I was going to go to graduate school." He considered a return to Davis, but he also visited the biochemistry department on the UC campus in Riverside. He liked what he saw, and ended up there, in the 'Inland Empire,' studying under Tony Norman. Norman is today a well-known researcher. In the late 1960s, he was just beginning to establish a reputation as an expert on vitamin D.[26] Adams remembers that "the entire Norman laboratory was working on the mechanism, the action, of vitamin D – vitamin D is really a hormone, it initiates all sorts of events associated with calcium metabolism." The topic of Adams' Ph.D. dissertation was the particular mechanism of calcium transport induced by vitamin D in the small intestine.[27] After concluding his thesis research, Adams opted not to embark on an academic career in biochemistry. He planned to go into industry instead, although no biochem students from Riverside had done so in recent memory. His advisor encouraged him. Adams says, "Norman had a lot of friends that worked in industry, so he knew a lot about it. He introduced me to some people."

---

[26] A.W. Norman, M.R., Haussler, T.H. Adams, J.F. Myrtle, P. Roberts, and K.A. Hibberd, "Basic Studies on the Mechanism of Action of Vitamin D," American Journal of Clinical Nutrition1969, April 22(4):396-411; T.H. Adams and A.W. Norman, "Studies on the mechanism of action of calciferol. I. Basic parameters of vitamin D-mediated calcium transport," Journal of Biological Chemistry 1970, September10, 245(17): 4421-31; T.H. Adams, R.G. Wong, and A.W. Norman, "Studies on the mechanism of action of calciferol. II. Effects of the polyene antibiotic, filipin, on vitamin D-mediated calcium transport," Journal of Biological Chemistry 1970, 245, 17:4432-42; A.W. Norman, A.K. Mircheff, T.H. Adams, A. Spielvogel, "Studies on the mechanism of action of calciferol. III. Vitamin D-mediated increase of intestinal brush order alkaline phosphatase activity," Biochimica et Biophysica Acta 1970, August 14, 215(2): 348-59; R.G. Wong, T.H. Adams, P.A. Roberts, and A.W. Norman, "Studies on the mechanism of action of calciferol. IV. Interaction of the polyene antibiotic, filipin, with intestinal mucosal membranes from vitamin D-treated and vitamin D-deficient chicks," Biochimica et Biophysica Acta 1970, 219(1):61-72.

[27] Thomas Henry Adams, "Vitamin D Mediated Calcium Transport," Ph.D. Dissertation, Department of Biochemistry, University of California, Riverside, 1969.

Adams received a number of employment offers, and seriously considered accepting a position as a research chemist at Smith, Kline & French in Philadelphia. Smith Kline was looking to staff a development team for an ulcer drug project. He ended up, though, in Orange County, at an arm of DuPont, one of about fifty scientists and engineers working to develop a new automated clinical analyzer system and disposable test packs. The group was looking for broadly trained chemists, and Adams fit the bill. He commenced work on the instrument reagent system. "It was enzymes and substrates, that kind of thing," Adams says, "fairly conventional clinical chemistry, but it had to be adapted, and we actually ended up having to invent certain chemistries that would do it, so I invented several different assays while I was there."[28] Adams stayed with DuPont for four years. He wasn't unhappy with the company, but he was ambitious and impatient. He explains that, in DuPont's structured corporate environment, he didn't foresee for himself the kind of career progress and upward mobility that he wanted to attain:

> DuPont is a fine company, but if you're there and you're a young person, as I was, you look around and you see that it's a very ordered situation in terms of advancement, that sort of thing. I was a senior research chemist and group leader by the time I left, but I thought I could eventually lead a program like that entire group, and wanted to do that, probably before I was forty, and I didn't see it happening there.

After four years with DuPont, Adams was contacted by headhunters looking for someone qualified to head up a diagnostics research group at the Hyland division of Baxter-Travenol in Costa Mesa, California. Hyland was a much smaller place, and

---

[28] Thomas H. Adams, "Method for the determination of amylase," U.S. Patent No. 3,879,263; filed September 6, 1973; issued April 22, 1975; Thomas H. Adams, "Process for measuring carbon dioxide content of the body fluid," U.S. Patent No. 3,974,037; filed February 1, 1973; issued August 10, 1976.

Adams perceived the job as "a situation where I thought I could do something," so he made the move. While at Hyland, Adams continued to build a reputation for technical brilliance, and learned a lot about, among other things, using enzymes to replace radionuclides as labels in immunoassays.[29] The first enzyme-based immunoassays were developed in the early 1970s.[30] They attracted attention from clinical laboratories because, although enzymatic reactions were not as efficiently or conveniently detected as radioisotopic emissions, they permitted the development of 'homogenous' assays – tests that did not require a separation step. In addition, enzyme usage eliminated radiation hazards, eased regulatory compliance requirements, simplified reagent handling, and streamlined waste storage and disposal procedures. Enzymatic tests were on 'the cutting edge' of immunoassay technology during the 1970s.[31] Adams stayed on top of breaking developments in the area, and later helped Hybritech develop enzymatic versions of the TANDEM assay.

Adams remained at Hyland for six years, and during that period, worked closely with Ted Greene, when Greene showed up in 1976, and with several research managers in the division who also later made their ways to Hybritech, through their connections to Adams and Greene. When Baxter announced its intention in the

---

[29] Thomas H. Adams, James P. Beck, and Robert C. Menson, "Method and apparatus for making novel particulate compositions," U.S. Patent No. 4,211,015; filed January 18, 1978; issued July 8, 1980; T.H. Adams TH, G.M. Ramsay GM, and G.B. Wisdom, "Enzyme immunoassay of albumin as an aid to the diagnosis of cystic fibrosis in the newborn human [proceedings]," Biochemical Society Transactions, 1979, 7, 5:1018-9; T.H. Adams and G.B. Wisdom, "Peroxidase labelling of antibodies for use in enzyme immunoassay [proceedings]," Biochemical Society Transactions, 1979, 7, 1:55-7.

[30] E. Engvall and P. Perelman, "Enzyme-linked Immunosorbent assay (ELISA). Quantitative assay of immunoglobulin G," Immunochemistry 1971, 8: 871-874.

[31] Syva marketed the first commercial enzyme-labeled assay in 1972. The test bore the 'EMIT' trademark – enzyme-multipled immunoassay technique.

summer of 1978 to move the Hyland division back to Illinois, Adams decided to explore his options: "I thought about it, and I'd spent a lot of time in Chicago because we had a manufacturing plant there, and I knew a lot about it, and it wasn't someplace that I wanted to go." After leaking word that he was available and willing to entertain offers, he again began fielding calls from headhunters, including one who represented Technicon, a clinical instrument manufacturer headquartered in Tarrytown, New York. Adams discovered that his services were in high demand. "During that entire period of time," he says, "people were proposing different things to me. Technicon was the leader in the diagnostics field, and they offered me the job of vice-president of chemistry research and development, at quite a bit larger salary and a lot more responsibility, so I decided to do that." Adams made the move to the East Coast, to direct R&D on reagent systems for Technicon's automated assay readers.

Shortly after getting settled at Technicon, Adams began receiving telephone calls from Ted Greene, who was attempting to commercialize hybridoma technology, first with Cytex Laboratories, and subsequently with Hybritech. According to Adams, Greene initially sought him out for technical advice – "asking me about this and that" – and then, late in 1979, finally started trying to talk him into moving back out to California to join Hybritech. This continued for six months. Adams was not interested. Greene had told him all about monoclonal antibodies while both of them were still at Hyland, so Adams understood what Cytex and Hybritech were trying to accomplish. "I knew," he says, "what the limitations of conventional antibodies were, and I thought that, with a good cell biology group, you could develop monoclonals that had the right specs, and that it could turn into a giant business because the

availability of antibodies was always a problem, because of the animals." Still, joining a tiny start-up company wasn't on Adams' career agenda. He hadn't heard any arguments that would compel him to give up his new, prestigious, and handsomely compensated position at Technicon, but he had at his fingertips a number of good reasons for staying put:

> I hadn't been at Technicon all that long, and my family had just relocated. Technicon was a neat company, and I was working for John Whitehead, who was the founder's son. His father, Jack, was still there. He was chairman, and one of the smartest guys I've ever met in the medical field. And they gave me a lot of responsibility. I was, at the time, thirty-five, and I had arguably the top job in the industry on the R&D side.

Greene was not deterred. He took advantage of every opportunity to pester his friend: "I went to the AACC [American Association of Clinical Chemistry] meeting in New Orleans, and cornered Tom in an oyster bar. I said, 'Tom you've got to help me do this.' He was then a vice-president of Technicon, probably making two to three times as much as I was, and he thought I was insane, but I kept hammering on him." Greene kept calling, and, on occasion, adopted some long distance guerrilla tactics:

> One time, I got so frustrated on the phone that I said, 'Goddamn it, Tom, I can't deal with this. I'm coming out there. Meet me at the airport.' He lived in Connecticut. And I went down to Lindbergh Field, piled on a plane, flew out to Kennedy, and he picked me up at the airport. We talked all night long. The sun came up and he took me back to the airport, and I came home. It was that kind of process to try to get this guy.

In the course of trying to persuade Adams to join Hybritech, Greene turned to another contact from Hyland for assistance, a gentleman named Bill Crean, who had worked in human resources. When Baxter began dismantling the Hyland division for relocation, Crean decided that he wanted to remain in California. He found a job with

American Hospital Supply Corporation and then shortly tendered his resignation at Hyland. At American Hospital Supply, he was rapidly promoted. He became a personnel director and was reassigned to a plant in Puerto Rico. Ted Greene tracked him down in San Juan, and explained that he was trying to recruit Tom Adams. Crean recalls:

> While in Puerto Rico, I got a call from Ted Greene about relocation, about how to relocate Tom Adams back from Technicon in Tarrytown, New York, I believe, to California. I gave Ted some advice on how to set up a relocation approach to bring people that were new hires to Hybritech. So, Greene actually used me a sort of a consultant, if you will, or an advisor.

Crean recalls being asked questions like, "If you were going to relocate someone, how would you do it? Do you pay for the house? The closing costs? The relocation expenses? Do you move the boat, do you not move the boat? So, I gave him some general advice based on the Baxter relocation policy and the American Hospital Supply relocation policy." In this way, Hybritech began adapting human resource practices from large, established companies to fit its start-up circumstances. Hybritech hadn't yet progressed to the point where it made sense to establish its own personnel department, so Greene used his industry contacts to educate himself. He tried to sweeten the deal for Adams to the degree that he could, but none of his efforts made much of an impact until Adams' situation was altered by unrelated events transpiring in Tarrytown at the highest executive level. In December 1979, Adams received some unwelcome news concerning Technicon's future:

> I got a call from my boss late on a Friday night, and he said that Jack had decided to sell the company, and Jack Whitehead owned 85% of Technicon, and it was worth, you know, several hundred million dollars. He was in his sixties, I think, and so there had been rumors

> flying around for a long time that General Electric, Johnson & Johnson, or Revlon were going to acquire Technicon. So, he said they were going to announce it on Monday morning. I said, 'OK, which company is it?' And he said, 'Revlon.' So, mentally, I left right then. GE or J&J might have been a different story.[32]

Around the professional circles in which Tom Adams traveled, Revlon did not have a good reputation. The acquisition didn't take place until May of 1980, but once it was apparent that Revlon would be moving in, Adams became more receptive to Greene's pleadings, and eventually succumbed: "When Ted called, I listened a little bit closer to what he was doing, that's what it was." In their conversations, Greene had always emphasized the technological challenges and opportunities that Köhler and Milstein's invention had created. "The way you deal with a Tom Adams," Greene maintains, "is you talk about the science and the technology, the ideas, new products, things we could invent, how we could do this or that, what the problems were." Greene had explained to Adams how monoclonal antibodies could be employed to improve solid phase IRMAs and ELISAs. The possibilities intrigued Adams, who enjoyed surfing on waves of technological change. It certainly wasn't the prestige of the job or the pay that motivated Adams to enlist at Hybritech. "I took a pretty big salary cut," he says, "to come back out here."

Adams arranged a move to San Diego in April, immediately after the Technicon deal was to be finalized. The news of Adams' impending arrival sent reverberations through Hybritech, especially when the firm's R&D teams learned of

---

[32] With proceeds from the sale, Jack Whitehead founded the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology. The Institute has become a leading center of genomics research. Jack Whitehead's son, and Adams' boss, John Whitehead, Jr., remains involved with the institute, and active in both business and philanthropy.

his status as a thought leader in the diagnostics industry. In Howard Birndorf's opinion, "Ted really made a tremendous coup when he recruited Tom Adams."[33] Greene was concerned about how the appointment would strike Bob Wang. Wang had just come into the company, and was providing Hybritech with some indispensable services in assay development. Greene knew that Wang prized autonomy on the job. Adams, who was to be his boss, was respected in the industry for his technical excellence, but was also known to favor an autocratic approach to project management. Greene wanted to prepare Wang for the organizational changes that he was sure Adams would implement:

> I'll never forget telling Bob. He said to me when I hired him, 'Look, are you going to hire a guy to run development, to run R&D?' And I said, 'Yeah, I probably am.' And he looked at me and said, 'Well, I don't know. There aren't too many people I could work for.' And I finally had to go to him and tell him, 'Well, I've done it, Bob.' I remember this was at a restaurant. I took him out to dinner. He asked, 'Who is it?' I said, 'It's Tom Adams.' And his response was 'Oh, well, that's OK, that's alright.'

Greene was relieved, and ecstatic to have someone like Tom Adams supervising the company's product development activities. "Hybritech was never the same," he says, "because now we had a real product development team." Gary David concurs. He believes that Adams brought to the firm, along with his technical expertise, a definite sense of commercial direction. He suggests that Adams's leadership consolidated and inured Hybritech's R&D program: "Tom came in, Adams came in, and got us focused on selecting an assay format, which was what we then rather quickly put our efforts on." Hybritech was set to tackle some formidable technical obstacles that remained in the way of the firm's product development goals,

---

[33] Fjermedal, Magic Bullets, p. 104.

and, then, to make some real commercial progress. In 1984, after Hybritech had marketed several successful monoclonal antibody-based diagnostics products, and had launched, as planned, an in vivo imaging and therapeutics program, Brook Byers commented on the early formation of the company: "Of these first main people, Ivor, Howard, me, Gary, Ted, and Tom, if any one of those pieces had not come along at the time they showed up, we wouldn't be here, at least to this degree of success."[34]

INDUSTRIAL DISCIPLINE

A week before Tom Adams took over as Hybritech's director of research and development, Ted Greene announced that all employees would be expected to be present at eight o'clock in the morning, and that the official company hours would henceforth be designated eight-to-five. The new schedule was not well received. In fact, Gary David recalls that "it caused one incredible explosion." Employees began arriving promptly at eight, as instructed, but "it was like one enormous wet blanket on the whole company." Hybritech's scientists had been working long hours. According to David, "Most people were not home before ten or eleven at night." It had not been expected, previously, that everybody would show up at an appointed time each morning. Hybritech had been running loosely, it had lacked regimentation, but Greene's announcement indicated that the atmosphere of the place was going to change. David doubts that Greene ever fully realized the effect of his proclamation, and is certain that he never intended it, but David reports that a number of workers at the firm developed "negative attitudes" in the aftermath, and he recollects trying to "calm people down." "I don't think the company ever recovered from it," he says. "I

[34] Fjermedal, Magic Bullets, p. 101.

thought then, and I think now, that the whole reason for doing it was to set us up for an Adams environment." The researchers went on, and the work at Hybritech certainly remained challenging and exciting, but the giddy sense of unadulterated, unfettered 'science for the pure fun of it' was gone for good.

When Adams arrived, he knew that he had a good technology with which to work: "Gary and Ted dreamed this thing up. They were the two inventors of TANDEM, and it was a good assay." He quickly learned, however, that before launching into development of the technology, he would first have to do some organizational work. The company, at that point, he says, "was Ted and a bunch of scientists." Adams recognized that the firm had collected a group of talented researchers, but also saw that "what they needed, early on, was to be able to focus on a product." Adams's first order of business was to get Hybritech's intellectual properties in order. That aspect of the program was in disarray because "there hadn't been any professional R&D person there at the beginning." Ted Greene admits that, "we were in total chaos in terms of patents and that sort of thing, because Gary was strictly an academic scientist." Adams's first priority was to get the patent issues straightened out. He found that not one of the company's laboratory notebooks had been signed and witnessed. Such documentation is standard operating procedure in the industry, and the oversight proved to be something of an embarrassment in later patent litigation proceedings.[35]

[35] The laxity with which the company's scientists approached intellectual property matters hindered Hybritech's case in an infringement suit brought against Monoclonal Antibodies, Inc., in 1984. Monoclonal Antibodies was a small Bay Area firm that employed the Hybritech technology with its own antibodies directed against its own antigens. The company was selling monoclonal-based pregnancy tests. "At the time," says Ted Greene, "we weren't very disciplined about keeping records or

In the course of setting Birndorf and Royston up in business in the fall of 1978, Kleiner Perkins had engaged the Los Angeles law firm, Lyon & Lyon, to provide the entrepreneurs with guidance and assistance regarding intellectual property. Tom Kiley was the attorney assigned to Hybritech, but he left Lyon & Lyon soon after to become general counsel at Genentech. After Kiley departed, the law firm turned its new biotech client over to Larry Respess. Respess was an organic chemist with a Ph.D. from MIT. After earning his doctorate, he joined the Air Force, and worked in the materials lab at Wright Patterson Air Force Base. When he left the military, he attended law school at George Washington University, taking night classes while working during the day in the Phillips Petroleum patent department. Following his graduation from law school, Respess worked as a clerk at the old U.S. Board of Customs and Patent Appeals, which is now part of the United States Court for the Federal Circuit. Finally, he moved to Lyon & Lyon. When Respess inherited Hybritech, late in the summer of 1979, he traveled down to San Diego to meet with Greene and Birndorf, but didn't hear from Hybritech again until April 1980. "Tom Kiley and I came down when he left," Respess remembers, "and we just sort of had an

---

anything else, so the first defense of that patent must have cost us two million dollars." See Hybritech Incorporated v. Monoclonal Antibodies, Inc., Appeal No. 86-531, United States Court of Appeals for the Federal Circuit, September 19, 1986. For a sociological analysis of the case, see Alberto Cambrosio and Peter Keating, Exquisite Specificity: The Monoclonal Antibody Revolution, Oxford: Oxford University Press, 1995, ch. 5. Cambrosio and Keating argue that the validity of the TANDEM patent rested, not on facts, and not on evidence demonstrating technological priority, but rather on contested interpretations of the identities of monoclonal antibodies and kinds of immunoassays, interpretations associated with distinct social groups, interests, and practices (e.g., immunoassay manufacturers competing for market share, expert witnesses from various scientific disciplines with differing opinions on the significance of monoclonal antibodies, and customers in clinical reference laboratories who judged the novelty and utility of diagnostic tests according to their own criteria). Ted Greene and Roger Ekins, an expert witness called by Monoclonal Antibodies, later debated these issues on the pages of Nature. See Roger Ekins, "A Shadow Over Immunoassay," Nature 1989, 340: 256-258; and Howard E. Greene, Jr. and Bradford J. Duft, "Disputes Over Monoclonal Antibodies," Nature 1990, 347; 117-118.

introduction, you know, 'Here I am to help you if you need help.' But I never received any requests to do anything for them until Tom Adams came."

When Adams arrived at Hybritech and got up to speed regarding the progress that had been made in the company's labs, he called Respess, introduced himself, and said that he thought Hybritech had made an invention. He requested a meeting with the attorney. Respess returned to San Diego and sat down with Adams, David, and Wang. "It was in a trailer," he remembers, "a temporary trailer pulled up in the parking lot of the La Jolla Cancer Research Foundation." Wang had prepared an extensive summary of the technology that explained how it worked , what the objectives were, and so on. Respess was already familiar with immunoassays. A few years earlier, Lyon & Lyon had been involved in a suit filed by Abbott against a small company in LA for infringing on Abbott's so-called 'Ausria' patent that protected an immunoassay for detecting the hepatitis virus. Lyon & Lyon represented Abbott, and Respess and Kiley had worked on the case together. With that background to draw upon, Respess took Wang's summary, and, later, data from the IgE project that Wang produced over the summer months, and wrote up an application for a patent on the TANDEM assay. The application was filed in August.

With intellectual property matters running on the correct track, Adams set about reordering Hybritech's development operation. By itself, Adams' designation as vice-president of R&D had created a dimension of organizational architecture that wasn't previously there. The new VP went further and implemented a formal reporting structure. "It wasn't organized at all when I got there," he explains. "I mean, these guys called themselves the junior woodchucks, you know, so all the

scientists reported to Ted directly. That was just unworkable, so I put together an organization out of the people that were there. We turned it into a more professionally run R&D organization." Adams attempted to introduce a modicum of industrial discipline. Blending academic and corporate cultures and building organizations around biotechnologies was mostly uncharted territory in the early 1980s, but Adams took the system that the academics had fashioned for themselves, such as it was, and worked to reshape it until it started to resemble a more or less conventional industrial model. Walt Desmond summarizes the operational changes that followed Adams' introduction to the company, from the perspective of a scientist at the lab bench:

> He added a little bit of industrial or business rigor to the way we operated. He introduced lab notebooks. We had to think about things like patents, you know, things that are really obvious from a manufacturing standpoint, standard operating procedures. Research meetings, where we talked about the science, became a little more formal, I guess. Well, just having him there made it different, and one major difference was that, obviously, there's a sort of organizational hierarchy, and it wasn't necessary to get together with everybody like it had been earlier. So, I mean, we didn't see, say, Ted Greene as much.

Adams' arrival freed Ted Greene to attend to the duties of the chief executive, which were varied, but eventually came to be dominated by fund-raising activities. Greene withdrew from direct participation in the firm's scientific projects. Adams assumed full control and responsibility in research and development. The immediate goal that the company had set for itself was the design of a diagnostic kit that made use of monoclonal antibodies and the TANDEM assay to detect IgE in serum. Hybritech's researchers had already established that the TANDEM assay was superior to competing formats. It was as accurate as any comparable test, and, in addition, was faster and more sensitive than conventional RIAs and IRMAs that employed

polyclonal antibodies. The practical development challenge, then, was to package the assay in a way that would offer these advantages, along with reliability, convenience, ease of use, cost-effectiveness, affordability, and competitive pricing, to customers in clinical laboratories. The company believed that hybridoma technology would permit it to scale up the production of superior, standardized reagents at costs significantly lower than those associated with the usual means of manufacturing polyclonal antibodies. Conventional methods entailed stabling horses and goats on ranches, immunizing and bleeding the animals, fractionating the serum, subjecting antibody proteins to harsh, damaging, denaturing purification processes, and then, for all of the trouble, still making do with insufficient quantities of highly variable and only partially distilled and useful reagent compositions. If Hybritech could figure out how to make diagnostic kits with monoclonal antibodies, then, despite its small size, it could enjoy some tremendous advantages in the marketplace.[36]

Hybritech's scientists had not yet settled on an assay format for the proposed kit. They had established that it would be a solid phase radioimmunometric assay of some kind, but they hadn't decided on a definite structural configuration for the product. They hadn't selected the specific material components with which the kit would be constructed, and they hadn't worked out the precise chemistries or procedural steps that would comprise the test. An important decision had to be made about the solid phase. There were many materials from which to choose: ceramics, metals, various natural and synthetic polymers, and composites. (Industrial chemists

[36] Hybritech still had to make use of animals, of course, but the company made murine antibodies. Mice require much less food and space than horses and goats. They can be maintained in laboratories.

had, at the time, begun attaching antibodies to all sorts of things for many different purposes). There were advantages and disadvantages associated with all of the possibilities, but Abbott's hepatitis kit utilized polystyrene beads, so Hybritech's research team had started with that option and had stuck with it. Gary David reports that, "We had been working with beads from the beginning. The initial intent was to come out with a bead assay, I believe, because, since we were targeting hepatitis initially as the first kit, we wanted to put out something the market was familiar with, which was a bead-based assay."

When the company decided to make the first TANDEM product an IgE test, however, the Hybritech scientists reconsidered. "I think it was there," David says, "that we backed off and started exploring other formats seriously as possible for commercialization." David and his colleagues began investigating methods employed by the competition in the new market that they were planning to enter, the IgE market. Kallestad Diagnostics of Chaska, Minnesota was selling an IgE test called Quantitope, a conventional, labeled-antigen, competitive radioimmunoassay that did not rely on solid phase separation. Pharmacia also had a competitive RIA called RIST, in which labeled IgE molecules were bound to sephadex, a synthetic version of a polysacchride, dextran. By 1980, the RIST assay had been largely displaced in the marketplace by Pharmacia's new, more sensitive and accurate test, called PRIST. The PRIST kit was based on a solid phase sandwich assay in which the 'capture' antibodies were attached to cellulose discs. It was a 'forward' assay that incorporated two separate incubation steps. Calbiochem-Behring was also marketing a new sandwich ELISA, Enzygnost-IgE, that used an antibody-coated tube as a solid phase, but which required three steps.

Hybritech identified Pharmacia's PRIST kit as the principal competitor against which its monoclonal-based test would have to compare favorably. PRIST was innovative. It was much faster than the competitive assays, simpler than the Enzygnost-IgE, and it was gaining market share.

David and his helpers looked at the paper discs used in the PRIST kit. They weren't particularly impressed. They decided to try CBNr-activated sepharose as a solid phase. Sepharose is the name of a brand of agarose, a form of micronized cellulose. CNBr is short for cyanogen bromide. Treatment with CNBr transforms hydroxyl groups on sepharose into imidocarbonate groups, which are then available for stable covalent linking with amino groups of proteins like antibodies. David, Wang, and Sevier were well acquainted with the properties of CBNr-activated sepharose. The trio had used the material as a solid phase in immunoassays at Scripps, and Hybritech's screening technique employed it as well.[37] The disadvantage of sandwich assays using sepharose as a solid phase was that they required a centrifugation step. The tiny particles holding the antigen-antibody sandwiches formed a suspension in the solution. This had to be compacted by force before being washed in the separation process. The Hybritech team knew that centrifugation would be inconvenient for customers, for technicians performing the assay, but they reasoned that centrifugation was a standard procedure in clinical laboratories, and they believed that a monoclonal IgE test using sepharose could compete with the polyclonal PRIST

[37] Robert E. Wang, E. Dale Sevier, Ralph A. Reisfeld, and Gary S. David, "Semi-automatic solid-phase radioimmunoassay for carcinoembryonic antigen," Journal of Immunological Methods 1977, 18: 157-164; G.S. David, T.H. Chino, and R.A. Reisfeld, "Binding of proteins to CBNr-activated Sepharose 4B," FEBS Letters 1974, 43, 3:264-266.

kit in the existing market. Above all, because they had so much experience working with sepharose as a solid phase, they expected that this format would be, by far, the assay that they could assemble, manufacture, and ship in the shortest span of time. Reaching the marketplace in order to begin generating revenues was an overriding concern. "Because of simplicity and familiarity with sepharose," David explains, "I think we were probably leaning in that direction."[38]

This was the situation when Adams arrived on the scene. He didn't like the idea. He insisted that the Hybritech team go back to beads. "They had developed the antibodies for IgE already," Adams recollects. "They were working on a two-site immunometric assay that used sepharose as a solid phase. I didn't believe that would be commercially successful because it required centrifugation, so we changed the developmental path a little bit by going to a bead in a tube assay." David recalls experiencing some minor discomfort with the decision, because it was not immediately clear to him how Hybritech was going to get the antibodies on the beads: "there were more unknowns that had to be worked out." His interest was piqued by the challenge, however, and he didn't mind deferring to Adams. "I don't recall any major rifts," he says. David now gives Adams credit for the eventual success of the company's first diagnostic product: "I think what Adams did was to see the tremendous advantage that coming out with the bead format would offer, and what the immunometric format would be in general. He put his foot down, and said, 'This is the way it's going to be. Do it.'" Wang corroborates David's recollections: "I think

[38] The simplicity to which David refers is not simplicity in using the kit in clinical contexts, but rather in manufacturing it.

he saw that we needed to come out with something that was really different, that had significant marketing advantages. He convinced Ted Greene of that." Making judgments of this kind was precisely what Greene had hired Adams to do, and, as it turned out the following year when Hybritech's IgE test was approved by the FDA, Adams hadn't let him down. His commercial instincts were true, and the product eventually did very well.[39]

Adams handed out the marching orders, and the company's researchers embarked on their mission to design a bead-in-a-tube kit. Bob Wang took the point position for the development team in the laboratory. Gary David recalls that Wang directed most of the tests and collected most of the data in the drive to put a product on the market: "Bob carried out the experiments that led to the TANDEM assay, and the TANDEM patent, and the first products." Wang remembers Adams' command regarding the assay format as a turning point. "When we dropped all the work on our first system," he says, "that's when I did all the experiments to generate the data for the TANDEM patent." The patented idea was reduced to practice in the course of the IgE product development process. Wang liked to work autonomously, but he

[39] A year later, when Hybritech began developing its first enzyme-based assays, Adams again insisted on taking a more difficult route at a technical fork in the road, because it led to products with greater commercial viability. In TANDEM-E tests, as they were called, analyte measurements or identifications were made from spectrophotometric or visual inspections of reactions that occurred when sandwiches including enzyme-labeled antibodies were exposed to a volatile substrate. Hybritech's R&D teams boiled the possible choices for the enzyme down to two – peroxidase or alkaline phosphatase. Assay sensitivity was more readily achieved using peroxidase, and again, in this instance, David and the other Scripps chemists at the company had experience with it and preferred it. With peroxidase, however, the assays required an additional time-consuming and inconvenient step. "I remember," says a Hybritech manager, "there was this duel going on between the research guys and the development guys, and the research guys kept trying to tell us, 'No, alkaline phosphatase is not going to be sensitive enough.'" Once more, Adams made the call: "'You've got to go with alkaline phosphatase. You're going to make it more sensitive.'"

appreciated Adams' decisiveness. He had gotten himself out of Scripps five years earlier and into industry because he disliked academic politics, and one of things that he disliked, in particular, about the academy was that "no one has the final word." In industry, by contrast, Wang proposes, "you've got a guy who pounds the table, and says that's it." Wang thought that this was the way to get things done.

'DID I SAY THAT RIGHT?'

So, the course was charted and Hybritech's scientists knew where they were headed. They soon discovered, however, that getting there would be no simple matter. In developing the IgE test, they were confronted by a number of technical complications, and a wide range of uncertainties – ill-defined problems with unknown causes, and solutions that would likely be discovered only after a good deal of experimentation and learning, if at all (just like 'real science'). Anticipating that this would be the case, Adams had already gone to work shaping the company's development processes in ways that would enable the company to isolate and focus attention on particular areas of need, in the industrial manner of doing things. He brought in a project manager to coordinate the various R&D tasks that could be identified at the beginning of the process. He wanted someone who was already familiar with the industrial development of radioisotopic immunoassays: "The first assay was ^{125}I labeled, so we recruited Russ Saunders, who had experience from Nuclear Medical Laboratories. Wang was already there, so those two guys kind of became the core of the development effort." Saunders had worked for Adams a few years earlier at the Hyland division of Baxter-Travenol in Costa Mesa. He was the third ex-Baxter person, after Greene and Adams, to show up at Hybritech as a

manager. Several more would shortly follow. "The reason they came after me," Saunders relates, "was that I had experience. First of all, they knew me. I was a good old boy. I had the experience they wanted, and that was developing radioimmunoassays in a commercial environment for a company that was successful."

Saunders was originally from West Virginia. He earned a bachelor's degree in chemistry from Bethany College, a small school in the Allegheny Mountains, and then took a sales job with the Celanese Chemical Corporation. He ended up working as a rep in Los Angeles, but discovered that he wasn't really cut out for sales, at least at that point in his life. He decided to go to graduate school, first at UCLA, and later at the University of Southern California. At USC, he was awarded a doctorate for work on alpha 2 macroglobulin, a large blood protein that serves various metabolic functions by binding proteolytic enzymes.[40] Afterwards, surveying what he viewed as a contracting environment for grants in his subfield, Saunders decided to go back into industry. He found a position with a small company in L.A. called Curtis Nuclear, and then learned about a job at Hyland in Costa Mesa. "Hyland was an exciting company at the time," he says, "doing a lot of research." He interviewed and was hired into a molecular biology group within the chemistry department that Tom Adams ran. "Adams was handling all of the chemistry out there," Saunders remembers. He recalls meeting Ted Greene, too: "I got to know him through the corporate development and marketing role that he played out there. He was from McKinsey."

[40] Russell Lee Saunders, "Studies of human alpha(2) macroglobulin: physical and enzyme binding properties," Ph.D. Dissertation, Department of Chemistry, University of Southern California, 1970.

Hyland was in the business of making antibodies for immunoassays, and had just started to get its feet wet in the diagnostic testing market. Almost immediately, however, in 1975, the company's feet started getting cold; the firm decided to shut down the assay development program. Saunders explains: "Clinical Assays at the time had developed a new technology where they were coating antibodies onto tubes, and they [Hyland] thought that was going to crush them." It turned out that the Clinical Assays method could not be used with many antigens, and did not pose the competitive threat that Hyland had feared, but the company perceived itself to be at a technological disadvantage as far as diagnostic kits were concerned. It did not aggressively pursue opportunities for growth in the area of immunoassays. Shortly after this episode, the company began pulling the plug on several other programs in what turned out to be preparations for the eventual reassignment of the division back to Chicago. Saunders sensed heavy weather in the air. He began looking for another job and latched on to Nuclear Medical Laboratories (NML), which was located in Dallas. He went to Texas to work with a chemistry group that was developing new radioactive compounds for use in a test for thyroxine: "It wasn't working, so I had to go down there and help with that, bail that out, and we did."[41] The test was very successful, the company was purchased by Warner Lambert, and Saunders was promoted to director of R&D.

[41] Thyroxine (T4) is the major hormone secreted by the thyroid gland. Levels of thyroxine found in the blood are indicative of thyroid function. T4 measurements, in conjunction with assays for thyroid-stimulating hormone (TSH) and thyroid-binding globulin (TBG), are widely employed by physicians as routine screenings for thyroid ailments. Millions are performed each year.

In the summer of 1980, Tom Adams called. He told Saunders about Hybritech and monoclonal antibodies, and asked whether he would consider making a move to San Diego. Saunders already knew about hybridoma technology. Warner Lambert had begun experimenting with monoclonals; NML had set up a small laboratory in Seguin, Texas to make them. But, according to Saunders, the technical capacities and insights possessed by his company did not compare with Hybritech's. At Warner Lambert and NML, he says, "we wanted antibodies for the current technology, so the radioimmunoassays that we had, which were all competitive binding assays, would work better. All we wanted to do was to make better antibodies, antibody that had a higher binding constant, or affinity, and to make a lot of it cheaper." It hadn't occurred to the NML researchers that monoclonals would permit the invention of new assay designs and diagnostic products that would be far superior, in both technical and commercial terms, to anything then on the market. Adams invited Saunders to visit San Diego. "We had dinner at Ted's house," he remembers, "and he and Tom convinced me that this was the place to be." It was the technological opportunity that he found most attractive: "I follow technology, and very recklessly follow technology. I don't consider the money I'm going to make, what kind of future might be down the road, my family, you know, I just follow the technology."

In fact, Saunders followed technological persons as much as technological ideas or objects. In this instance, he was following Tom Adams and Ted Greene: "I had tremendous respect for Tom Adams," he says. "I knew he was good. I mean, the man is brilliant. And Ted Greene, I knew, had tremendous potential. So it was those two guys, plus the fact that it was a new technology. Monoclonals, I knew, were hot.

So I told my wife I was going to take the job." Saunders didn't actually know very much about what was going on in Hybritech's laboratories. Before arriving in San Diego, he was basing his decisions mainly on his faith in Adams and Greene. They declared that the firm did, in fact, have control of a revolutionary technology, and that the start-up had a genuine shot at survival and success: "They just told me they had a blockbuster technology. I don't recall whether they got into details at the time. I don't think they did because I was working for a serious competitor." But Saunders believed, without hearing the details.[42] He now admits that he didn't appreciate the significance of hybridoma technology in the field of immunoassay development, and that when he was finally introduced to the company's trade secrets in confidence, he required a period of adjustment to assimilate and become comfortable with the new 'paradigm.' "I was indoctrinated," he says, "with the old competitive binding philosophy. I don't think I fully comprehended the TANDEM assay until we got around to seeing what it could do, and trying to resolve some of the problems it had. In fact, Tom Adams had to keep reeducating me, every once in a while, on the horsepower of that thing and what they could do with it."

When Saunders first arrived at Hybritech in September 1980, he was impressed with the high quality of the scientific team that he found hard at work there: "They had people like Joanne Martinis, Gary David, Walt Desmond, Bob Wang – an excellent group of people. I don't know how they pulled all of these people into one

[42] For a discussion of the grounds for such beliefs, see Steven Shapin, A Social History of Truth: Civility and Science in Seventeenth-Century England, Chicago: University of Chicago Press, 1994, ch. 6. Shapin argues that scientific progress and scientific communities everywhere depend crucially on blind faith in things and trust among persons.

place. And they all got along pretty well. Richard Bartholomew was another fellow with a lot of talent."[43] Saunders understood that his job at Hybritech was to help Tom Adams inject some industrial rigor into the operation, to coordinate the efforts of a talented but relatively undisciplined collection of academics, and to organize a cohesive product development team. He wasn't asked to bring any special scientific expertise to the project, and he claims that, coming into the company from a conventional industrial environment, and from work on conventional assay technologies, he didn't really possess any to contribute. "I just knew what it took to put these kits together," he explains, "and I knew how to evaluate their performance, but as far as all of the technology that went into it, they had it all." Saunders was a planner, a technology manager. "My background in product development was finding out what had to be done, and who had to do it, and how long it would take, and to set up a process. That was my training, so that's what I did when I showed up." The scientists were a bit leery when first informed that Saunders would be stepping into a supervisory role, and their apprehension grew when their new boss made his entrance:

> I rolled in here with a car from Texas, a great big old Oldsmobile 98, two city blocks long. It was an older car, and I stuck a pair of bullhorns that I had from Texas on the hood of this car, and parked it right in front of the trailers that they had at the time. And I saw all these faces looking out the window. There was Walt Desmond with his beard, and Joanne Martinis and Gary David, all peering out the window. And they

[43] Richard Bartholomew was an immunochemist who came to Hybritech from Scripps. Gary David knew him and persuaded him to join the company very early on. Bartholomew and David screened the antibodies that went into the first diagnostic assays. They later worked together on conjugation chemistry and antibody engineering projects in the firm's therapeutics R&D programs. Bartholomew's abilities seem to impress just about everyone who collaborates with him. Gary David says "Richard Bartholomew is probably the person with the best memory of anybody I have ever known." Sam Halpern, a nuclear medicine specialist at UCSD who teamed with Hybritech personnel on numerous cancer imaging and therapy projects, says, "Richard Bartholomew is absolutely brilliant. He learns at an incredible rate. The only problem that Richard has is that his mind works so fast that the rest of us can't keep up with him. I really love little Richard."

> were frightened to death that some redneck had pulled up there. They brought me in as director of product development, so they were very concerned about who this guy was. So, I was known as Tex for quite a while after that. They found out that I wasn't what they thought I was.

The group quickly warmed to the personable Saunders, and Saunders likewise found Hybritech's scientists to be an amenable bunch, on the whole: "I had very little problem getting them to understand what had to be done." He recalls that they accepted the new regime with good humor: "As they heard all these new industrial terms, the jokes went on endlessly. Joanne Martinis was great for this. Every time they picked up a new word that they heard the business people saying, she'd adopt it, and use it over and over, and ask, 'Did I say that right?'" The scientists had become wed to their technological projects, so they adapted to the new environment, the new ways, and the new lingo. "Of course," Saunders adds, "Tom [Adams] sort of ruled with an iron fist, too, so that was a convincer, and because of that, it would make my job a lot easier." Saunders smoothed the transition. Adams' manner was brusque, but Saunders' approach was easy, relaxed, and congenial. It was a 'good cop, bad cop' routine. Adams was VP of research and development, but, in the labs, Saunders played an important role in getting a bunch of very independent people with distinctive, sometimes abrasive, personalities to work together and work happily, for the most part. He was particularly mindful and cautious in maneuvering around Bob Wang, upon whose technical expertise he relied heavily in the development process, and with whom he was required to consult on a daily basis. "Number one," he says:

> I realized that his IQ was about thirty points higher than mine. Number two, he was in there working on that technology for several months before I had, and doing a pretty damned good job of it, and I was supposed to come in and tell him what to do? As far as I was

> concerned, he was a 500 lb. gorilla, and you know, I just handled him very delicately. But working together like that, we became pretty good friends.

Saunders assembled an effective team from an unlikely cast of characters. He was able to elicit cooperation from individuals who might otherwise have clashed, naturally, and perhaps fiercely. Wang and Martinis, for example, were especially well known for both their extraordinary abilities and their tendencies to adopt combative postures in defense of personal interests and ideas. "Bob was probably one of the more strong-willed people," Saunders notes, "but very talented and very bright. Joanne Martinis was also very strong-willed and very intelligent. She had strong convictions and expressed herself." It all worked out. In fact, Wang attests that:

> It was a lot of fun. I mean, we really enjoyed it. In spite of the personality conflicts, the people were pretty accepting of each other's difference. There was a real sense of camaraderie and teamwork at the time. Now, if you look back at that group, and you kind of wonder why, because it was really eclectic, and that's probably being too mild when you look at the personalities.

Saunders chalks it up to the extraordinary circumstances of the start-up. The industrial rigor that Adams sought to impose on Hybritech's R&D operation required the subordination of individuals. Affiliated persons were expected to recognize that obligations to the company came before individual prerogatives. They were expected to preserve in the daily activities of the firm a kind of civility that might not have been possible to maintain in many academic contexts. In academic settings, avoidance rather than cooperative interaction might have ensued with this particular group of people. But Saunders explains that, in the case of Hybritech:

> Everybody wanted the same thing, and they worked together, even when some people didn't get along real well. When you've got a small

> company, and everybody has stock in the small company, they all know that their careers and their financial well-being depend on that. And you're not going to get that unless you cooperate with each other. They all knew that and it worked.

The spirit of cooperation at the firm was perhaps especially pronounced at that point in time because Hybritech was running out of money again. In September, just as Saunders was arriving, Greene had to arrange for a loan from the Bank of America to make payroll. It was fortunate for Saunders, and Hybritech, too, that his faith was so strong. He had come out to San Diego by himself, while his family remained in Texas tying up loose ends before following him. When he found out about the firm's financial condition, he called his wife to say, "'You might want to stay there. You might try to sell the house, but be a hard liner on it for a while.'" The property remained on the market for a time. "I was," Saunders remarks, "a big Texas landowner for several months." Rumors about the impending failure of the company began to circulate around the local scientific community. According to Bob Wang, "people would ask things like, 'Hey, what's happening to Hybritech? I hear that you guys are running out of money and are going to go under.'" The company's plight was not as desperate as it might have appeared to outsiders. "At the time," Wang says, "people didn't understand the process of venture capital." Kleiner Perkins was not about to let Hybritech founder while it was still making technical progress toward goals with potentially large payoffs. After Tom Adams came into the company, Ted Greene turned his attention from the TANDEM assay to the company's finances. Hybritech was spending money at an alarming rate. The board of directors met to

discuss ways to raise additional funds. A plan was formulated and Greene set out to raise $10 million.

At the top of Greene's list of possible investors was Henry Hillman of Pittsburgh, PA. "Henry, at the time," Green relates, "was one of the wealthiest people in America. In fact, when the Forbes listing would come out, he was usually about number eight on that."[44] Hillman was the son of John Hartwell Hillman, Jr., a steel tycoon who made his fortune by establishing and building the Pittsburgh Coke & Chemical Company. Henry graduated from Princeton and then went into the family business. He took it over in 1959, and expanded his holdings by making good investments in light industry and real estate. Hillman put money into Kleiner Perkins' first venture fund in 1972, and learned about Hybritech from Tom Perkins. Greene remembers the fund raising effort and discussions with Hillman about the company that eventually crystallized the deal:

> We were pitching people like Elf Aquitaine, because the oil companies were flush. The oil industry was just awash with cash. You know, we had Standard of Indiana, and they were making some investments. And finally, one day, Henry Hillman says to me, 'Look, we'll do the deal.' I said, 'You will?' He said, 'Heck, yeah, we'll put all the money in.' Well, of course, as soon as that happened, I mean, once you have a well respected lead investor who says, 'I'm in, I'll do the whole deal if nobody else wants to,' then all of a sudden we had everybody lining up, wanting to do the deal.

Brook Byers then encouraged Greene to extend invitations to institutional investors, including universities with endowment funds. With Hillman and Standard

---

[44] By 2004, Hillman, at eighty-three years of age, with a net worth of about $3 billion, had descended to #58 on the Forbes 400 list of the richest Americans, far behind Bill Gates and Warren Buffett, at $46.6 billion and $42.9 billion, respectively. Forbes also ranked Hillman #176 among the 'World's Richest People' in 2004.

of Indiana already firmly committed, Stanford University, Rockefeller University, and the University of California were easily convinced, and each put in significant sums. Soon, the deal was over-subscribed. Hybritech had pledges totaling $13 million, and closed the round in November 1980.[45] Hillman's CRF Investments, Inc. of Wilmington, Delaware purchased 2,000,000 shares of preferred stock in Hybritech at $3.75 per share, a 26.9% stake in the company, and Stephen J. Banks, a vice-president of the Hillman Company, took a seat on Hybritech's board of directors.[46] The situation was never really a dire one, but the episode was educational for all involved in the operation of the firm. The young academic scientists working in the company's laboratories had remained confident and mostly unruffled by the shortfall, but they were made aware of the rate at which they were spending, and the rapidity with which the firm's position, and their personal paychecks and jobs, could become precarious. Greene and Adams took the opportunity to impress upon the researchers the importance of economy, and to impose stricter spending controls. Walt Desmond describes the atmosphere within the company at the time:

> We were just about to run out of money, and it was kind of dramatic, but there was no real feeling of panic or anything. The feeling was that we were trying to get money in various places, and that we were going to get it. It made us realize, I mean, it was a funny kind of situation because there's this huge pot of money and you just burned it. At some point, maybe after Tom Adams came, we had to have a budget, and people said, 'Oh, a budget? You mean we have to plan what we're going to spend?' It was a different situation.

---

[45] "Then, immediately," says Greene, "no sooner than we got the money, we started thinking about doing the IPO." For high-tech start-ups, raising money is a perpetual concern and a nearly perpetual process. The notion of taking the small, unprofitable company public became more seductive and much less preposterous – to Greene, Brook Byers, Tom Perkins, and the rest of the Hybritech board – a few weeks earlier on October 14, 1980, when Genentech raised $35 million from its initial stock offering.

[46] Hybritech, Inc., "Initial Public Stock Offering Prospectus," October 28, 1981.

In these circumstances, Saunders immediately began doing what he had been hired for – he started planning. He composed an R&D project profile, an internal company document, dated October 1, 1980, that became the bible for the product development team.[47] It included notes on the chemical composition, physiological functions, and clinical significance of the IgE molecule, comments on competitors' tests, and preliminary, qualitative comparisons of these assays with reverse and simultaneous procedures that Hybritech had developed over the summer months. Another section detailed the steps comprising Hybritech's assays, and listed the reagents and structural components to be included in the kits, along with equipment not supplied in the product that clinical laboratories would need to conduct tests. It estimated the costs of raw materials, labor, and overhead in the preparation and assembly of the kits.[48] The profile also cited relevant patents that needed to be compared to the technology in the Hybritech assay system, and regulatory issues that would likely concern the FDA during the product approval process.[49] Finally, the document laid out a master development schedule, and targeted the end of January 1981 as completion date.

---

[47] Russ Saunders, "Hybritech R&D Profile; IgE Radioimmunoassay," October 1, 1980.

[48] The expected cost per unit came to $27.10 ($5.10 for antiserum, beads, other materials, and waste; $7.00 for the labor involved in producing the antiserum, preparing the chemistry, iodinating the antibody, and assembling the kit; and $15.00 of overhead for facilities, administrative support, etc.). Saunders projected a market price somewhere between $100.00 and $175.00 for each kit (including the apparatus and reagents in quantities sufficient to run one hundred tests).

[49] The patents were assigned to Pharmacia. They covered a process for coupling antibodies to insoluble polymers via cyanogen bromide activation (U.S. Patent No. 3,645,852), and an immunoassay method for the quantitative determination of IgE in solution (U.S. Patent No. 3,720,760).

Four months was not much time in which to develop a new product, especially one that incorporated an untested technology, but, given the rate at which the company was spending money on R&D, there was no time to lose. The schedule broke down the development process into forty independent tasks, and delegated responsibilities for each to individual team members. The assay format had already been decided. Hybritech was going to manufacture a solid phase, bead-based, simultaneous radioimmunometric assay. Saunders was to monitor overall progress and adjust the project schedule as necessary, evaluate the market and the competition, compile and disseminate relevant literature to the development team, keep track of the quality and storage of antibody pools and other material stocks, perform raw material tests, secure clinical samples, oversee applications of analytical methods in testing protocals, produce and maintain quality control records, and assist in various other areas. Gary David and Richard Bartholomew were to screen anti-IgE monoclonals (which Joanne Martinis and Walt Desmond would deliver from cell biology), and David would be responsible for the radioisotopic labeling of the soluble antibody.[50] Bob Wang was designated team leader for the project. He was to configure the assay hardware and devise the chemistry for the solid phase, develop methods for stabilizing the antibody stock, radiolabels, and standards (partially purified antigen preparations used to calibrate the assays – to the extent possible with peptide and protein antigens), and document carefully the performance of Hybritech's IgE test with those offered by the

[50] To tag antibodies at Hybritech, David adapted techniques that he had developed at Scripps for labeling antigens. See G.S. David and R.A. Reisfeld, "Protein iodination with solid state lactoperoxidase," Biochemistry 12: 1014, 1975.

competition, because that data would be crucial for the regulatory submission.[51] Finally, he was to begin developing methods to scale up production techniques. Cole Owen, who had recently been hired from Johnson & Johnson as the company's first director of marketing, was to draft (with Tom Adams) the 510(k) submission to the FDA, along with the package inserts and labels, and handle all of the printing.[52] The interdisciplinary product development effort was organized. The industrialists had arrived and whipped the academic scientists into shape. Saunders credits Greene and Adams, in tandem, as it were, for the necessary overhaul of the firm, for the platooning of the academics:

> Ted knew that he had to head them in a different direction, but I think it took Tom, because he had the technical background, plus the business experience, to put the thing together. Those two guys were a big reason for the company's success, the combination of those two, Tom and Ted. One or the other, I think, could have messed it up, but the two of them together, it was perfect.

SCRATCHING THE SURFACE

By October 1980, Hybritech had several anti-IgE antibody-producing hybridoma cell lines growing in its cell biology laboratory. The firm hadn't yet marketed any of the antibodies as research products, but IgE was one of the molecules that had been selected for this purpose early in 1979. So, for a year and a half, the

---

[51] On problems attending efforts to standardize immunoassays for large, heterogeneous molecules, see Roger Ekins, "Immunoassay Standardization," Scandinavian Journal of Clinical Laboratory Investigation supplement, 1991, 205: 33-46; and Ulf-Håkan Stenman, "Immunoassay Standardization: Is it Possible? Who is Responsible? Who is Capable?" Clinical Chemistry 2001, 47, 5: 815-820.

[52] Officially, Owen was the director of marketing, though there wasn't yet a marketing a department, and no one reported to him. "I wasn't directing a hell of a lot," he says. "There wasn't anybody else there." Paul Rosinack had been hired a few months earlier, in May of 1980, from Johnson & Johnson's Ortho subsidiary as vice-president of sales, but his activities were mostly external. He was involved in setting up distribution networks.

company's scientists had been immunizing mice with human IgE, extracting B-lymphocytes from the animals and fusing them with murine myelomas, culturing hybridoma clones that produced anti-human IgE immunoglobulins, and then investigating and characterizing the immunochemical and biological properties of these antibodies. When Hybritechs's strategy for the development of a diagnostic product shifted away from hepatitis, the firms's cell biologists redoubled their IgE efforts. At the same time, the company's immunochemists began looking for antibodies that would work in a radioimmunometric assay to detect IgE in solution, and could be incorporated into a commercially viable diagnostic kit. According to Walt Desmond, "It was a lot more complicated than just getting two antibodies that worked." The monoclonals had to do more than simply attach themselves selectively to IgE molecules. They had to perform well within the context of the assay, as chemical reagents, and under conditions dictated by the material and physical requirements of the kit. In addition to being 'smart' (i.e., specific) and 'sticky' (i.e., avid – exhibiting high affinity for the antigenic target), they had to be durable and reliable.

The TANDEM system required two different anti-IgE antibodies that would work well together. The company scientists sought individual antibodies that displayed both high affinity and low cross-reactivity, and pairs that targeted antigenic determinants in ways that would not interfere with the formation of antibody:antigen:labeled-antibody sandwich complexes. One antibody in a pair had to adhere to the solid phase, to the bead, and, with the unique peptide chains comprising the variable region at the end of its free arms, capture the IgE molecule at a specific

antigenic determinant. The soluble labeled-antibody had to accept and carry its radioisotope without fumbling it, and then combine with IgE at a different determinant on the molecule. This epitope had to be located sufficiently distant from the first so as not to prevent the antigen from becoming anchored on the solid phase. The selection process was critical. Gary David and the immunochemists would try to find antibodies that were at least adequate, if not optimal, for the designated tasks. Luckily, when Bob Wang and this development team started experimenting with assay formats in the summer of 1980, the company found out that it already possessed some good ones. It was not a simple or straightforward process, but Wang was able to make the assays work. If no suitable pairs had been available among the antibodies that the firm had already produced, then the immunochemists would have had a lot of work to do. They would have had to confer with the cell biologists in order to identify cell lines likely to produce two workable immunoglobulins. They would have had to prepare antigens, conduct fusions, and then screen again for antibodies that exhibited the desired characteristics – particular traits that would translate into acceptable performances under the conditions of the diagnostic test. Finding good antibodies could have taken a long time. The project might have been set back months. But the company was fortunate to have antibodies on hand, and the work went forward without delay.

The company was also fortunate to be able to assign Bob Wang to product development tasks. Wang got into the life sciences after being drafted in 1966. When his name was called, he dropped out of school at UC-Berkeley, and awaited a summons to enter the military. As it turned out, the order never came. He returned to

school and started enrolling in chemistry courses. "Before," he says, "I had always been in engineering. It was a family pressure thing. If you know Asian families, there's this big thing to become engineers or doctors, medical doctors. I certainly wasn't going to be a medical doctor." Wang majored in biochemistry, and did well in his major courses, which he enjoyed, but his overall G.P.A. was below 3.0. "I had fun in college," he says. Wang's advisor at Berkeley was Daniel Koshland, a world-renowned and controversial biochemist, and editor-in-chief of Science from 1985 to 1995.[53] At the end of his senior year, Koshland asked Wang if he wanted to go to graduate school. Wang said, "'Sounds good to me.'" He told Koshland that he preferred to stay in California. Koshland suggested UC-Riverside, a school with an outstanding biochemistry department. Wang didn't know the place, but his advisor made the decision easy for him:

> I got into the department without ever taking the Graduate Record Exam or even applying, and I got accepted with a fellowship. They sent me a letter saying 'Congratulations, you're accepted, dude, please respond.' And I sent a letter saying, 'I accept.' I'm sure Koshland called them up – Randy Wedding was the chairman of the department – to say, 'I've got an undergrad student who would be good in your graduate program.'

Wang arrived in Riverside in 1969, just as Tom Adams was leaving. In his cohort was Dale Sevier, who would become a life-long friend and colleague. The pair received Ph.D.s in 1973, and wound up together again later that year in postdoctoral

[53] Koshland gained notoriety for proposing the 'induced fit' theory of enzyme-substrate interaction. He argued that the active sites of enzymes conform flexibly to substrates – they are reconfigured in chemical bonding. Koshland's 'hand in glove' idea eventually displaced the 'lock and key' theory of Emil Fischer, the 1902 recipient the Nobel Prize in chemistry, that had long stood as a basic dogma in the field of enzymology.

research positions at the Scripps Research Institute in La Jolla.[54] There, working with Gary David in Ralph Reisfeld's laboratory, they accumulated a good deal of practical experience in immunoassay design. In 1975, Wang left to acquire some more at a start-up company called International Diagnostics Technology (IDT), located in Santa Clara. He hadn't cared much for Scripps, and he and his wife had wanted to move back home to the Bay Area, with their two sons, in order to be closer to their families. The company was less than a year old, and Wang was only the fifth employee. He calls IDT "a good learning experience for me." He found at the company plenty of opportunities for analyzing and diagnosing problems in immunoassay technologies. In one instance, he discovered that signals generated by the firm's proprietary assay system were mostly artifactual. "They didn't want to hear that," he says. "The guy who was in charge of R&D at the time gave me a lot of crap for it, but we spent the next three months proving that what I told them was right."

The company had developed a process to immobilize an antibody chemically on a material called polymethylmethacrylate, a kind of film. The assay called for an immunoreaction between enzyme-labeled antigen and the antibody on the film, and, with the addition of a substrate, the production of measurable fluorescence. The polymethylmethacrylate was exposed to a sulfuric acid etching process that, in theory, formed functional chemical groups to cross-link antibody covalently. In practice, however, as Wang discovered, the etching created a roughened surface with superb

---

[54] Ernest Dale Sevier, "Glycoprotein uridine-diphosphate N-acetylglucosaminyl transferase in Armoracia rusticana," Ph.D. Dissertation, University of California, Riverside, 1973; Robert Wang, "Studies on yeast phenylalanyl transfer-ribonucleic acid synthetase," Ph.D. Dissertation, Department of Biochemistry, University of California, Riverside, 1973.

non-specific binding properties. When the assay was run, there was competition between labeled antigen and non-labeled antigen for space on the film (along with anything else in solution that might have been competing with it). When Wang devised controls for the test, he found, to his dismay, that it didn't matter whether or not he applied antibody to the polymethylmethacrylate: "I said, 'We've got a problem here, boys.' And they said, 'No, you've done it wrong.' I said, 'No, I didn't. I repeated it several times. You don't need antibodies to run this assay, which tells me that you're looking at an artifact.'"

To rescue the project, IDT's R&D team came up with a fix that incorporated the problem into the solution. They adopted a reverse format for the assay. The first step became a liquid phase reaction in which the labeled-antigen was mixed with soluble antibody. The polymethylmethacrylate film solid phase was then employed as a non-specific adsorbent to separate out antibody that had bound labeled-antigen. With uncontrolled non-specific binding taking place, the procedure couldn't advertise much accuracy or sensitivity, but, according to Wang, the company had little choice but to reconfigure the test as a reverse assay. The technology simply hadn't advanced far enough to make the assay work as originally envisioned:

> There wasn't anything else to do at the time. We worked on a lot of surface modification things at the time trying to graft functional groups on and do chemical linkage of antibodies to surfaces, but, at that point in time, the plastics industry hadn't come up with the right substrates yet. Non-specific binding is always a big problem, but today, the plastics industry has developed some good substrates for coupling, or chemically coupling proteins or macromolecules to the surface specifically.

Wang stayed at IDT for nearly four years. The German diagnostics firm Boehringer Mannheim eventually purchased the company, and a new director of R&D appeared on the scene. Wang didn't see eye-to-eye with the man, and their interactions were marred by conflict. Wang thought he was dishonest. "He lied to me," Wang says, "and I won't accept that." Wang quit. He walked away from IDT without a job, but soon had offers to join Genentech, a tiny biotech firm in South San Francisco staffed by a bunch of scientific hotshots who were some doing things with DNA, Pago, a new reagent company in San Mateo, and Bioscience Laboratories down in Van Nuys, in the San Fernando Valley, where Dale Sevier was working at the time. Wang also received an invitation from Calbiochem, a reagent maker in San Diego. Behring had just purchased the company and was planning to establish an immunodiagnostics operation on the West Coast. Jeanne Dunham and others had been dispatched from New Jersey to California to help set it up. This sounded something like a start-up situation to Wang. He had enjoyed the intimate, unstructured entrepreneurial atmosphere at IDT, and he considered San Diego a nice place to live, so he opted for the Calbiochem position.

In San Diego, Wang got in touch with Gary David, who told him all about Hybritech. When Wang learned about hybridoma technology, he understood immediately that it would be used to improve immunoassays. He saw that hybridoma techniques would enable the production of superior, highly specific antibodies without the laborious and inefficient purification treatments required to make polyclonal mixtures useable. Just as significant for the new solid phase assay systems in which Wang had demonstrated expertise, was the fact that hybridoma technology would

permit the manufacture of unlimited supplies of standardized immunoreagents. Generating antibodies in sufficient quantities was a universal problem for manufacturers of reagent excess, solid phase assays. The objective with assays of this kind is always to immobilize as much specific antibody as possible on the solid phase, in order to increase the immunoreactivity of the substrate, and with it, the accuracy and sensitivity of analyte measurements. Wang clued instantly into the opportunity and tried to make Calbiochem's new immunodiagnostics program an early mover into monoclonal-based products: "I got my boss to go over to talk to Hybritech about monoclonal antibodies and what they might be able to do for us, because we were trying to develop ELISAs [enyzme-linked immunosorbent assays] at that time."

When Ted Greene initiated Hybritech's product development drive late in 1979, Gary David, along with Dale Sevier, who had returned to San Diego in August, pressed him to talk to Wang, and then, to extend a job offer. Wang was interested, and said so, but he felt compelled to stay at Calbiochem for a full year. According to his employment contract, leaving earlier would have obliged him to repay Calbiochem for the expense of his move from the Bay Area. Hybritech offered to pick up the tab, but Wang elected to wait. He didn't want to leave Calbiochem in the lurch. After helping the organization prepare for his departure, he finally made it to Hybritech on March 1, 1980. When he arrived, he felt right at home in the start-up's unstable, still somewhat eccentric, and occasionally frenzied environment.[55] He had already learned how to

[55] In the early days of the company, the scientists, as a group, were thoroughly disinterested in, and perhaps incapable of, establishing and maintaining a conventional corporate façade – despite the new industrial order. Bob Wang tells a story to illustrate, one among many in Hybritech lore that are told and retold in order to convey a sense of the informality and the relative lack of pretense that characterized the place. This particular story is about Walt Desmond. Wang says, "Walt is a great guy,

operate in that kind of atmosphere, and he enjoyed it. Casting lots with start-ups was risky, but he was just twenty-eight years of age and not overly concerned about what might happen if the company cratered: "I was young enough that I wasn't too worried. I could always get another position."

When Tom Adams announced that Hybritech's first diagnostic kit would be comprised by a bead-based assay, and Russ Saunders doled out the constitutive tasks of the project to individual members of the development team, the key technical problem fell into Bob Wang's lap. Saunders recognized that Wang, by virtue of his talent, training, and experience, was the person to handle the solid phase substrate processing. Wang was assigned the chore of developing a method for linking anti-IgE antibodies onto polystyrene beads covalently. This was not an easy thing to do. Saunders relates that "the literature was full of people, you know, trying to do it, coupling proteins to solid surfaces in all different kinds of ways. All I know is, from my experience, coming from NML, was that anybody who was trying to do it covalently was always having problems." Saunders wasn't sure that it could be done: "There were some technical problems initially that scared the heck out of me."

The prevailing thought in the field was that the linkage had to be handled very delicately. According to Saunders, "the only thing that seemed to be working was to coat them [the antibodies] very gently onto plastic tubes, like Clinical Assays was

---

OK, but he lives with what appears, to other people, to be disorganization. I mean, his desk would just be like, you'd look at it and you'd think that someone had rifled through all of his papers and just left a big mess, but that's just the way he was. One Halloween, Gary David went and got this fake cobweb and he taped it over his desk, and it looked great. It looked like no one had been there for hundreds of years. Walt loved it so much that he left it up for a long period of time – weeks, months. And every time he wanted a paper, he would gingerly reach underneath the cobwebs and pull out this piece of paper that he wanted."

doing, and that didn't work very well for larger antigens." IgE, an antibody protein, was a massive, gargantuan antigen.[56] Hybritech was attempting something that would not have occurred to many others in the field. Saunders says, "Nobody, I think, would have thought that you could take a polysytrene bead, chemically activate it, activate the antibody, and stick it on there to get that antibody sort of functional." Getting the antibody attached, and still intact and immunoreactive, was half the battle. Having the fixed antibody capture and maintain its grip on a bulky double-antibody complex through a washing step without eluting was the other half. That had not been accomplished before. Consequently, no one participating in the project at Hybritech was surprised when tests of the first experimental chemistries resulted in failure. And no one was particularly surprised when repeated attempts to coat the polystyrene went awry. Tom Adams recalls: "We had big trouble trying to put the antibodies on the beads."

Eventually, Wang was successful. He developed a process for modifying the beads that involved treating them with a number of different acids – sulfuric, nitric, and hydrochloric – sequentially. The procedure formed the necessary chemical groups on the styrene surface, and the R&D team was able to couple functional antibody proteins securely and reliably to the solid phase. The company had solved a very important and very difficult processing problem, and it had come to possess another new and valuable piece of proprietary technology. Presumably, it had further

[56] The molecular weight of IgE is about 200,000 daltons. Most of the molecules for which Hybritech developed TANDEM diagnostic tests were considerably less. The target of the best-selling kit, for example, prostate specific antigen (PSA), a serum marker of prostate cancer, has a molecular weight around 30,000 daltons.

extended its lead over its competition. On schedule according to Russ Saunders' plan, but unexpectedly, nonetheless, the chemistry for the solid phase substrate had been worked out in a period of less than three months. Saunders notes that the achievement was enabled by the invention of hybridoma technology. The company was able to select monoclonals that could take a chemical beating, be coupled covalently with the sterically active portion of the antibody still oriented outward, physically, in a functional manner, and be mass produced in quantities sufficient to coat the bead thoroughly, to make it highly immunoreactive. This could not have been accomplished with mixtures of polyclonal antibodies. "We lucked out in many ways, in my opinion," says Saunders.

IEF-373 and IED-227

With the solid phase chemistry in place, the R&D team was able to configure the rest of the kit and start testing it. The objectives were to make sure that all of the assay's components, reagents, and procedures were dependable, and that the device met the performance specs that the FDA would likely require for approval in its regulatory review, and customers would likely demand for approval in the marketplace. Wang put the assay through its paces and found some bugs. After his experience at IDT, he was especially vigilant for the possibility of non-specific binding. He tested and discovered that, "Sure enough, it made a difference whether or not you used antibody or didn't use antibody, but you could still generate a lower quality standard curve, a much lower quality standard curve, by not putting any antibody in." So, there was evidence of some 'unauthorized' binding of reagents to the solid phase. Those issues had to be sorted out and resolved. Wang then detected

another, potentially calamitous problem, as well. This one had to do with antibody-antigen interactions. The two antibodies selected by the company for use in the IgE test, called IEF-141 and IEF-373, had been chosen for their high affinity, lack of cross-reactivity, and hardiness, and they appeared to work well.[57] But there was trouble with one of them, and Bob Wang was uniquely equipped to uncover it – because he had allergies.

The R&D team was gearing up to begin clinical studies that the company expected would demonstrate to the FDA the accuracy and dependability of its new product. The standard against which the Hybritech test would be judged was the performance of other allergy tests that the agency had previously approved. The principal burden of a 510(k) submission – which the company hoped the FDA would accept as appropriate and sufficient in lieu of a far more elaborate PMA (pre-market approval) application – is to show the equivalence of a new medical device with industry standards. In order for Hybritech's IgE kit to cross this regulatory hurdle, the results of clinical studies conducted with the Hybritech test would have to match, within some reasonable margins of variance, results derived from other tests on the market. Hybritech's technicians were prepping to compare the company's kit with Pharmacia's PRIST test and Kallestad's Quantitope. They planned to use each to measure IgE levels in blood drawn from the same samples. If there was consonance in

[57] In the nomenclature of the Hybritech antibody library, the first letters indicated the antigen, so in this case, IE stood for IgE, immunoglobulin E. The last letter indicated the number of the fusion – A through Z represented fusions one through twenty-six that produced positive clones. The numerical portion of the designation referred to a particular line of cells. So, the IEF-141 antibody was a specific anti-human IgE murine IgG taken from a specific colony of hybridoma clones (#141) plated out from the fifth fusion (F) of two 'parent' cells – a murine myeloma derived from one of the various lines that the company had acquired, and a murine lymphocyte extracted from an animal after immunization with human IgE.

the results, then the company could make a strong case for permission to take its product to the marketplace. "If not," Russ Saunders wrote, in an internal company memo, "and even if Hybritech is superior, we will most likely have to spend more effort proving such a case."

In shakedown runs before the critical trials, Wang and his colleagues on the Hybritech product development team were testing each other's blood in order to compare the different kits. ("At the time," Wang explains, "the industry wasn't that sophisticated in regard to legal issues"). Wang knew that he was sensitive to many different environmental allergens, and he knew, from testing with the Pharmacia kit, that he had a fairly high level of IgE circulating in his bloodstream. 'Normal' IgE levels range from 5 to 500 IU/ml [international units per milliliter]. Measurements of the molecule in Wang's blood consistently gave readings between 800 and 900 IU/ml. These figures were just about what Wang expected. But with Hybritech's monoclonal reagents, the IgE in Wang's sample registered under 100 IU/ml. "That, of course raised the red flag," Wang remarks. "We did some dilution studies and found out that we had what is termed the 'high dose hook effect' in my specimen."[58] Samples with IgE levels much higher than Wang's – 2,000 IU/ml and above – had been tested with the Hybritech device, and no hook effect had appeared. The readings had been elevated, just as they were in the PRIST and Quantitope tests. The Hybritech scientists concluded that one of the selected monoclonal antibodies must have been

[58] Diluting serum and lowering concentrations of antigen can prevent antibody saturation and permit accurate measurements. In tests for certain analytes, 'prozone' effects and falsely low readings are common; in these, dilution protocols are often run as routine checks. Naturally, it is preferable from a marketing standpoint to minimize validation procedures where possible.

cross-reactive with a specific antigenic determinant on IgE molecules in Wang's blood, and that immunoglobulins binding at this site were somehow interfering with the formation of immobilized antibody:antigen:labeled-antibody 'sandwiches.' Not all of the analyte bound with radio-labeled immunoglobulin was being captured on the solid phase. Some of it was being lost in the wash before counting, and, in Wang's case, at least, the test was producing grossly attenuated figures.

An investigation led the company scientists to believe that when the assay was run, the IgE in the sample was saturating the soluble IEF-373 antibody, the one carrying the radiolabel. Apparently, IEF-373 was an anti-idiotype antibody – it recognized the specific IgE molecule that had been used to immunize the mouse, along with an epitope common to some undetermined percentage of the general antibody population in the IgE class. Hybritech's researchers did not know, and couldn't guess without conducting much more research, how widely distributed was either of these particular determinants. In any case, IEF-373 did, evidently, display some affinity for an epitope that, among all of the samples that Hybritech had tested, was displayed only on the surface of molecules found in Wang's blood. But, if Wang's allergies produced this result, then the allergic responses of others might, too. Presumably, some unknown, but potentially significant portion of the patient population would generate IgE molecules displaying this same determinant when exposed to allergens. And because IEF-373 was mildly cross-reactive with it, the reliability of Hybritech's allergy test could not be assured. It was not clear that, in the Hybritech test, one IU/ml measured in any given sample would necessarily be the same as one IU/ml in the next. The IEF-373 antibody was not going to work. It

exhibited a high affinity for IgE, but it was not a good antibody for quantitative diagnostic purposes. This unforeseen development placed Saunders' timetable in jeopardy. The company had to come up with a different antibody to take the place of IEF-373. "It was a mad scramble," Wang remembers. "We said, 'OK, let's go back and test all other positive clones." There was no guarantee that a substitute could be found. The company had only a few ready for evaluation.[59] If none performed adequately in the assay, and in combination with IEF-141, then the project would come to a full stop. A delay while cell biology cultivated a new monoclonal antibody for the test, or a new pair, would have devastated the firm financially.

As it happened, a few quick trials showed that the company did have a viable substitute on hand, an antibody called IED-227. It lacked the high affinity of its predecessor, but it had enough, and it was not cross-reactive. Using IED-227 as the radiolabeled antibody eliminated the high dose hook problem. It did not interfere with the activity of IEF-141 on the solid phase. Hybritech had been very lucky once again. The company had been planning to see sell IgE antibodies as research products. That's why it had maintained a store of some orphan IED-227 clones in liquid nitrogen. The hybridomas hadn't been developed for the diagnostics project, and no one knew if the immunoglobulin they secreted would be of any use, but they happened to be available, and Wang and the rest were grateful when IED-227 was tested and found to work:

---

[59] At the time of its IPO, in October 1981, the company announced that it had developed eleven anti-IgE monoclonal antibodies. See Hybritech, Inc. "Initial Public Stock Offering Prospectus," October 28, 1981.

> If we didn't have the additional clones, if someone had discarded them, because they said, you know, 'We don't need them,' we would have been up the creek. But they had saved these old clones, and we went back and screened whichever ones were positive. I think there were about five or six of them that we were able to go back and look at.

The company had lost just a couple of months. It could have been much worse. The trouble had induced a bit of anxiety, but it was educational, in Wang's estimation, and not fatal – it culminated with an accomplishment for the company's R&D team: "We learned a lot about the process, and those were the two antibodies [IEF-141 and IED-227) that ended up going out on the market as the first Hybritech product, the first TANDEM product."[60] The development team's studies confirmed that the kit no longer featured the same high degree of sensitivity or the same precision that it had previously with IEF-373, but, in the market for allergy tests, customers don't usually care about a test's capacity to detect IgE at very low concentrations. In most cases, they want to be able to tell when patients have a lot of it floating around in their blood. "Fortunately, in this particular product," Wang explains, "it wasn't an absolute necessity to have the sensitivity that we had with the other antibody." He still marvels at the good fortune of the firm in this sequence of events: "What are the chances, you know? The guy in charge of developing the product – his specimen

[60] Jeanne Dunham served as Hybritech's materials manager until 1982. She reports that when the manufacturing operation started keeping its own antibody stores, the lesson of the IgE crisis wasn't forgotten, or, at least, the habitual practice of holding onto spare antibodies wasn't abandoned. Hybritech kept just about all of the monoclonals that it manufactured, although external auditors could never, apparently, comprehend why. Dunham relates how "the only grief I got about inventory levels, because I always tried to keep them down low, was in the antibodies themselves. The auditors couldn't understand why we had so many thousands and maybe even hundreds of thousands of dollars in inventory in antibodies, not understanding that the antibody is so specific, and you make it once and you may never be able to make it quite the same way again, so we always tried to keep large inventories of that on hand, and they always gave me grief about that."

raises the red flag? You've got to have luck in this, alright? And it's got to come at the right time."

The timing permitted Hybritech to escape some real trouble at the FDA. When Wang and his colleagues in development discovered that IEF-373 wasn't going to work, the company was just a step away from calling in the regulators: "We were at the starting gate," Wang says, "ready to pull the trigger on this, to set things rolling." At the time, Hybritech was eyeing a ninety-day review period for a 510(k) submission. After the application was filed, the FDA would have three months to look over the data and claims. If, by the end of that period, the agency had not issued a rejection, or an order to wait while more information was gathered or outstanding problems were resolved, then the company would be clear to ship its product, to start generating revenues and building market share. Hybritech had been anxious to move the process along. Naturally, the company wanted to enter the marketplace as soon as possible, so it could make some money. It also didn't want to give the FDA time to ponder at its leisure whether it ought to reject, categorically, claims for the equivalence of monoclonal antibody-based assays with existing polyclonal tests on the market. Hybritech sensed that the agency was on the fence, deliberating about whether to accept a 510(k) notification or require a PMA for monoclonal diagnostics. Hybritech intended to submit the former, and the sooner, the better.

It turned out to be a good thing, however, for the company to be slowed down by Wang's allergies. Had the complication with IEF-373 appeared in formal clinical studies, it would almost certainly have ended the chances of taking a monoclonal antibody-based diagnostic kit to market after just a standard 510(k) review. The

approval process would have immediately become far more difficult, costly, and time-consuming. But that disaster was averted, thanks to IEF-373's affinity for Wang's immunoglobulins. In fact, the application that Hybritech eventually submitted managed to turn this technical weakness of monoclonal-based systems into a rationale for granting regulatory approval. It represented Wang's accidental discovery of the high dose hook effect, and the firm's subsequent rejection of IEF-373, as the outcome of a purposeful, standardized selection process: "It was determined," the company reported cryptically, "that IEF-373 inhibited the reaction of ^{125}I with insoluble IEF-141 somewhat."[61] The close call was transformed into evidence to support claims of the product's equivalence. Although crossreactivity was much more likely to cause problems in polyclonal tests, Hybritech likened the process of substituting IED-227 for IEF-373 to the purification of polyclonal antibodies. The company wrote that "the [monoclonal] antibodies chosen for the TANDEM™ assay for IgE react in a manner similar to [polyclonal] reagents laboriously purified for use...."[62]

The FDA didn't accept the assertion without question. The company was very careful with the language of the submission, but the novelty of monoclonal antibodies was difficult to ignore. Given the agency's inherent conservatism, the firm did not want to portray hybridoma technology as a revolutionary advance – that would have provided an excuse for the FDA to rule that only the most thorough review could

[61] Hybritech, Inc., "TANDEM™ IgE Kit," 510(k), reference #K8029913A, La Jolla, CA, April 30, 1981.

[62] Hybritech, Inc., "TANDEM™ IgE Kit," 510(k).

justify the introduction of the new product.[63] In his development plan and schedule, Russ Saunders had recommended that the company say as little as possible about hybridoma technology: "The monoclonal antibody aspect may have to be played down for the 510(k). We should only indicate that it is another way of preparing antibodies."[64] Later, when defending the TANDEM patent in the courts, Hybritech would argue that the use of monoclonal antibodies constituted an original invention, a conceptual departure from prior art.[65] In the regulatory context, however, the company maintained just the opposite – while monoclonal antibodies were improved reagents, the new assay was fundamentally the same as others already being used in clinical laboratories. A lot was at stake for Hybritech in the FDA's response to this line of argumentation.

At first, it appeared that the agency was not going to buy it. The trouble with the IEF-373 antibody was a case of cross-reactivity, but it was also a case of over-specificity. As Hybritech soon learned, the possibility of clinical errors due to the over-specificity of monoclonal reagents is what troubled the FDA most about the company's new product, and the use of monoclonal diagnostics, generally. Even after purification, it is impossible to maintain strict surveillance on the binding of polyclonal antibody mixtures. The cross-reactivity of polyclonal reagents cannot be controlled; it can only be managed. False positives in polyclonal diagnostic tests were

---

[63] Wang still complains about the foot-dragging: "The FDA is very cautious. For them, it's safer not to approve anything. And if it wasn't for pressure from Congress, they probably wouldn't approve anything."

[64] Russ Saunders, "Hybritech R&D Profile; IgE Radioimmunoassay," October 1, 1980.

[65] U.S. District Court, Northern District, California, Hybritech v. Monoclonal Antibodies, Inc., #C-81-0930, August 28, 1985.

a problem with which physicians, clinical laboratories, and the FDA had learned to live. But occurrences of cross-reactivity were dramatically curtailed with the use of monoclonal antibodies, because monoclonal antibodies exhibit 'exquisite specificity,' and, as clones, they are naturally standardized. It is possible, using monoclonal antibodies as probes, to characterize with precision the structural features of molecular entities of all sorts, and it is sometimes possible, using monoclonals, to triangulate the exact locations of the determinants to which the antibodies adhere on molecules and cell surfaces. For these reasons, the mass production of monoclonal antibodies with hybridoma technology represented a boon to researchers exploring life at the cellular and molecular levels. Monoclonal antibodies were tools that permitted scientists to explore aspects of biological structures, functions, and processes that previously had been out of reach, or impossible to find. Their specificity and their homogeneity made them useful for identifying molecules of interest, reliably, across a wide range of contexts, against a wide range of backgrounds.

As far as medical diagnostics were concerned, however, the FDA was worried that monoclonal antibodies would be too specific, that they would not be appropriate for the detection of common analytes exhibiting high degrees of molecular variability. A monoclonal, might, for example, be very effective at selectively targeting a particular molecular subtype, but fail to recognize relatives in the same general molecular family. Or, a monoclonal might, in most cases, identify and quantify analytes of a broad class, but still underepresent or fail to identify concentrations of a minor subpopulation within it. Testing errors of these sorts are extremely unlikely with polyclonal antibodies, but they become legitimate concerns with highly specific

reagents. Gary David recognized and acknowledged the problem: "If you determine that your target is heterogeneous and exhibits microheterogeneity, affinity for one population of antibodies will be different from the affinity of another population, and your quantitation data will be off."

Hybritech addessed the issue in its 510(k) submission for the IgE product, and tried to explain to the FDA that the screening and selection process was crucial to the reliability of the test (while attempting, simultaneously, not to draw undue attention to the significance of the monoclonality of reagents to the accuracy of the TANDEM assay). The problem of overspecificity is obviated as long as constant determinants – those not subject to allotypic variations throughout a population – are selected as targets. Because monoclonal antibodies permit the identification of distinct antigenic determinants, it is possible to select epitopes common to all representatives of an antigen class. "Initially," says David, "we just needed to run enough samples to show that it [overspecificity] wasn't a major concern." The Hybritech scientists compiled the data, Tom Adams wrote a cover letter, and the 510(k) notification was mailed to the FDA's Bureau of Medical Devices in Silver Spring, Maryland. The company then started counting down the ninety-day review period. Ted Greene remembers:

> We were waiting and waiting and waiting, and we got down to about day five, and we're starting to wonder, 'What's going on here?' Adams happened to be in Washington, so he stopped by the Bureau of Medical Devices and, unannounced, called on the guy who was evaluating it. And he walked into his office, and the guy says, 'Oh, we've decided to put all monoclonal antibody devices in Class III."

The Class III designation meant that a PMA would be required. Class III products were subject to a much more thorough and rigorous review. A Class III

approval process at this late stage in the development of the Hybritech product would have cost the company a lot of time and money that it simply couldn't spare. The firm felt that it had to announce a steady stream of advances in order to keep money flowing from investors. Reports of failures or major setbacks would test the faith of financial backers. No one at the firm wanted to perform these sorts of experiments. Greene relates that when he was informed of the FDA's position, his first reaction was to panic, and then, when his mind had cleared, his second thought was to beg:

> We went nuts. I got on an airplane and flew back there. I can remember meeting with the head of device evaluation, literally in tears, saying, 'You'll bankrupt us. You'll put us out of business.' I said, 'We'll work with you. We won't market the product, but we'll do anything to show you that you don't have to worry about this technology.'

Greene's appeal initiated a round of negotiations between the company and the regulatory agency regarding the status and administrative treatment of in vitro monoclonal antibody products. The company went to great lengths to reassure the FDA about hybridoma technology and monoclonals. Says Greene: "We showed them all of our confidential stuff. We helped them write a whole series of QC specifications." Wang remembers that:

> We ended up having to go back there, giving seminars to them, and just educating as to what monoclonal antibodies were, and, I mean, today it would seem ridiculous, but they were afraid of some unforeseen problems arising by substituting polyclonal antibodies with monoclonal antibodies. So, they were very slow to approve our application.

When Hybritech started supplying experimental data and other information to the FDA on the production and selection of monoclonal antibodies for incorporation into radioimmunometric diagnostic assays, the firm began looking for, and finding,

some allies and advocates within the agency. One official, in particular, a man named Nino Hippolito, was especially helpful. Hippolito was situated in a position of some authority at the Bureau of Medical Devices. Tom Adams flew back to Washington several times to meet with him. On one occasion, Wang traveled to Banff in the Canadian Rockies to chase him down at a cancer meeting. There, he spoke with Hippolito for an hour about Hybritech's plight, and, then, having completed his mission, got back on a plane to return to California. The San Diegans were dogged in their attempts to court Hippolito and gain his trust. Eventually, their efforts paid off. Hippolito became favorably disposed toward the technology and the company. He helped Hybritech educate his agency colleagues and bosses about the advantages of monoclonal antibodies and the potential pitfalls, as well. Hybritech's new industrialists had understood the importance of cultivating the right social connections. Wang tells of Tom Adams reporting to Ted Greene about Hybritech's lobbying efforts in Washington, and about the company's relationship with Hippolito:

> Ted Greene is real big on Ivy League graduates, OK? I remember Tom Adams was telling Ted, 'Oh, yeah. The guy there, Nino Hippolito, is in charge of this and that, and he's from Columbia.' And Ted goes, 'Oh, good! An Ivy League man!' Tom Adams looks at him kind of funny, and says, 'No, Colombia, South America.'"

CLEAR

At the end of May in 1981, in the middle of a late afternoon TGIF bash at Hybritech, just before the Memorial Day weekend, Ted Greene received a phone call. It was the head of the Bureau of Medical Devices, calling from Washington with news about Hybritech's 510(k) notification for the IgE test. He told Greene that the agency had declared the TANDEM™ IgE kit substantially equivalent to other commercially

available allergy tests. Greene says, "He was as excited as we were: 'We did it! You're clear! And in fact, can you put some slides together for us? The commissioner would like to present to President Reagan how we have expedited this new technology.'" Cheers went up in San Diego, and celebrations went on into the night. Wang remembers an overwhelming sense of relief: "We were close to having a major setback there, and we pulled the rabbit out of the hat." Hybritech had been obliged to expend a lot of time and energy in order to secure regulatory approval of its product, but it was all worthwhile, and not just because a Class III designation and a PMA application had been avoided. Much more had been accomplished. The company had helped to shape the way in which the FDA understood and treated monoclonal antibody products. Hybritech had, in effect, taught the agency how to make monoclonal antibodies and how to use them in diagnostic products, according to its own standards. It was costly, but the company had been able to influence the regulators' thinking about the firm's technology. And there was another benefit, too, as Ted Greene points out. Hybritech, for all of its effort, had put itself ahead of the competitive game it was playing: "The good news was that by the time the next guy came and, you know, submitted his 510(k) for a monoclonal antibody kit, he gets this pile of requests from the FDA about clonal stability, and about all this stuff, and they all go 'Aaagh!!!'"

The company had become familiar with the FDA's bureaucratic protocols, it had established personal relationships at the agency, and, with more TANDEM diagnostic products soon to enter the development pipeline, it had learned how it could expedite the approval process in the future. Gary David comments: "There was a lot

of dialogue with the FDA, and we ended up getting our first product approved. And then, as the others came in, delay for approval time got shorter and shorter and shorter as the comfort level went up." Hybritech had acquired valuable experience, knowledge, and organizational skill. Greene derived special satisfaction from the fact that his little company had been the first on the scene with monoclonals, and had managed to pull off an entrepreneurial coup. With an innovative and superior product on the market, Hybritech had registered a score against mighty Abbott and other industry giants. In the recent history of the diagnostics business, some small firms had been innovative, but they hadn't been able to sustain themselves autonomously. Against large corporations, and in just about every respect apart from creativity, small, undercapitalized operations were hugely disadvantaged in the management of expensive product developments and regulatory affairs. After getting the green light for the TANDEM IgE kit, Hybritech remained cash poor – despite the millions it had secured from investors – but Greene believed that hybridoma technology had rebalanced the scales of power in the industry. He speculates: "If Abbott had been the first one, and the FDA had come to them and said, 'We want to make this a pre-market approval,' they would have said, 'We think you're right. That's a good idea.' Right? Because all the little guys would be kept out."

Hybritech had made it to the marketplace with a competitive product. The IgE kit wouldn't make the company rich, but the company had set a goal for itself and had accomplished it. It had moved forward – it had done what it had needed to do in order to sustain itself. But the technical accomplishment was not purely the result of innovative scientific and engineering work carried out on the top of laboratory

benches. It had emerged from the formation of innovative practices and an innovative organizational culture. Hybritech had evolved, and the company now had a much better idea of how to proceed toward its next objectives. Hybritech was good, technically, but it had become better, organizationally, commercially, too. Now, it was disciplined. The company achieved its success when people like Jeanne Dunham, Tom Adams, Russ Saunders, and Bob Wang showed up to donate their funds of industrial experience to the operation and transform it. The product development effort had escaped a series of close calls with commercial, financial, technical, and regulatory hazards. These could have seriously impeded the firm's progress, or perhaps sunk it altogether, but they didn't. Hybritech had been lucky, and it had been prepared to take advantage of its second chances when they appeared.

The firm was still relatively small, relatively loose, and mainly science-driven. For the scientists, the environment and the technology remained exciting, challenging, and unpredictable – working at Hybritech was still nothing like working at Abbott, for example. The hybrid combination of science and business, of academic and industrial ways – the process of putting together something new – had created an atmosphere that was novel and fun. But if the company was going to survive, it would have to keep making technological progress. And that would require continued social, cultural, and organizational change. Hybritech's work had just begun. The scientists had just been introduced to the rough and tumble of the business world. The invention of the assay, Ted Greene says, "that was the easy part. I mean, you know, great ideas coming up everywhere, put in a little money, you know, it doesn't take much. You don't have to face the realities of the FDA and product organization, but then all of

sudden, things start to grow, and the investors start to depend on your performance...." Greene had an inkling of what success would mean for Hybritech – it would have to grow, and soon be wracked by more transformative and disruptive changes.

The TANDEM IgE kit turned out to be a good product. It was a commercial success. Clinical laboratories liked it, and purchased it. Technically, it had a lot going for it. A journal advertisement touted its attributes:

> TANDEM™ – IgE Kit, an immunoradiometric (IRMA) assay for the quantitative determination of total human serum IgE.
>
> A simultaneous two-site immunoradiometric assay with procedural simplicity and convenience now achievable by the use of two different monoclonal antibodies (mouse IgG) to two separate antigenic sites on the human IgE antibody.
>
> TANDEM™ is simple.
>
> No discs.
> No centrifugation.
> No multi-incubations.
> No reagent preparation or reconstitution.
>
> TANDEM™ – The New Method of Choice![66]

The earth didn't shake when the new kit was introduced. As Bob Wang concedes, the IgE test "was not a great medical contribution." Yet, it had demonstrated the utility of monoclonal antibodies and the advantages of the TANDEM assay system. That was precisely what the company had intended when it opted to enter the allergy testing market rather than take on Abbott with a hepatitis test. Of the TANDEM assay, Ted Greene says: "I think it was that basic concept

[66] Hybritech, Inc., "TANDEM™ IgE Kit," 510(k), reference #K8029913A, La Jolla, CA, April 30, 1981.

which really got us rolling and by the time the biotech market took off, the fact that we actually had a product differentiated us strongly from everybody else." The assay and the kit were modest innovations in diagnostics, but their historical significance has little to do with the immediate economic, technical, or medical benefits that they afforded to Hybritech or its customers. In retrospect, these accomplishments were stepping stones for entrepreneurs who later played important roles in the growth of the San Diego biotechnology. Their impacts would ramify as Hybritech grew, and as the local biotech industry began to take shape.

X. BIG TIME

> You will do the greatest service to the state if you shall raise, not the roofs of the houses, but the souls of the citizens: for it is better that great souls should dwell in small houses than for mean slaves to lurk in great houses.
>
> Epictetus

SCALING UP

In 1981, Hybritech began to grow explosively, out of necessity. The company was preparing to manufacture its IgE diagnostic test at high volume, and to develop new kits to take to market. All of the firm's operations had to expand. The cell biologists needed to make more antibodies, the immunochemists were required to screen and test them, and the product development team had to get them to work in assay devices. The company's manufacturing personnel were seeking assistance from each of these groups as they struggled to scale up production processes. And the sales and marketing people, meanwhile, were busy setting up distribution networks and educating both themselves and their customers about monoclonal antibodies and their uses in clinical diagnostics. There was a lot of work to be done. Looking back, Ted Greene remembers, "We were hiring people all over the place." In addition to the departments that were already in place, Hybritech started assembling groups to handle a variety of other business functions as practical needs for them arose. Separate units eventually established within the company included, for example, quality assurance and control, clinical and regulatory affairs, corporate development, legal affairs,

facilities management, human resources, finance and accounting, investor relations, purchasing, and shipping and receiving. It wasn't long before all the trappings of a conventional small corporation fronted the firm's laboratories.

Initially, however, the areas of the company that grew the fastest were R&D and manufacturing. The IgE kit required the attention of just about everyone in the company simultaneously, but, once its design flaws were corrected, it then belonged mostly to manufacturing (although manufacturing personnel would regularly seek out the developers and the reagent scientists to consult with them about problems they were experiencing in scaling up antibody production and assay chemistries). The cell biology and immunochemistry groups turned their attention to other projects. They eventually pursued numerous and varied lines of research, but, early on, they focused mainly on preparing new antigens, hybridoma lines, and monoclonal antibodies for the development of additional in vitro diagnostics tests.[1] After the first test was packaged, the process became partially routinized. The assay format remained basically the same – all of Hybritech's products until 1984 utilized the TANDEM bead-in-a-tube design – but each antigen and antibody exhibited its own peculiarities and introduced unique technical difficulties. The immunization, hybridoma screening, and radio- and

[1] Walt Desmond tells about projects in cell biology: "We were always working on other methods of production, like human antibodies, using human lymphocytes, and in vitro production, rather than growing in mice." Human antibodies would have been preferred to immunogenic murine globulins for injectables. A substitute for the messy method of harvesting antibodies from ascites fluid probably would have been welcomed by the technicians who extracted and purified the stuff. The cell biologists examined 'hollow fiber' culture systems as possible alternatives. These grow antibodies inside fibrous tubes or cartridges in bioreactors. In the early 1980s, however, the technology was new, relatively expensive, and users were having problems with infections, so the mice stayed on for a time. Hybritech did eventually get rid of them, but not until Eli Lilly had purchased the company. Then, Desmond reports, "We settled on kind of the simplest, the most straightforward – fermenter culture, big stirred pots of cells that are used universally for production of microbial products, bacterial and fungus, things

enzyme-labeling processes therefore remained critical steps in the development of each test. Sometimes, emergent problems required innovative solutions, and only rarely did a project go off without hitch, so, development procedures were constantly being adapted and refined.

Still, with the basic assay template in place, the work proceeded rapidly. The Food and Drug Administration approved the company's IgE kit at the end of May 1981. By the time of Hybritech's initial public offering of stock just five months later, at the beginning of November, the FDA had already approved three additional kits.[2] These detected prostatic acid phosphatase (PAP), human chorionic gonatropin (HCG), and ferritin. (When elevated, PAP suggests the presence of metastatic prostate cancer; HCG at high concentrations indicates pregnancy; ferritin is an iron-storing protein – depletion is a symptom of anemia). The development operation had become the center of the company, and it was running with the throttle wide open. The TANDEM kits were good products. Customers wanted to buy them, so Hybritech was scrambling to get as many of them out on the market as possible, as fast as it could manage. In the midst of this rush, the development team was coping with a good bit of organizational dishevelment. Bob Wang says:

> We jumped from like ten people in product development to thirty, and it was very difficult to absorb that many people all at once. We had a number of people transfer from cell biology and research, and we hired quite a few new people, Ph.D. level people, to be group leaders, and it was a real challenge to manage everything. We ran into a few barriers. It was one of those phases. Start-up companies go through growth

---

like antibiotics and vitamins and stuff like that. So, those processes were adapted to mammalian cell cultures, and hybridomas specifically."

[2] Hybritech, Inc., "Initial Public Stock Offering Prospectus," October 28, 1981.

> phases, and the dynamics of the company change, and that was one of those times when the dynamics of the company really changed, I think.

By exploiting hybridoma technology and monoclonal antibodies, Hybritech was rapidly becoming an innovative player in the clinical diagnostics business. It was also swelling, and pushing people at an increasingly frenetic pace. Russ Saunders tells a story about the purposeful character of the company's haste at the time. In the late summer of 1981, he was at Hybritech on a Sunday afternoon, working against a deadline on the 510(k) submission for the TANDEM HCG kit, the pregnancy test. He detected some errors in the application that needed correction. Saunders tried to phone Ted Greene at home to ask for an extension. He was informed by someone at the Greene residence that Ted was out on his boat for the day. Saunders was then surprised to get a rapid call back: "Ted must have had a ship-to-shore set up because I received a call from his home telling me to fix everything on Sunday – not even one day delay! Since we didn't have a word processing system, we spent the rest of the day into the evening making artistic pencil corrections on page numbers, etc., that looked like typing." Saunders mailed in the submission, but was a little irritated: "I thought that Ted was being very silly until later, when we received the FDA approval the same day the IPO package was to go out. The approval gave a big boost to the credibility of our public offering. I never challenged Ted again."

With products moving through the development pipeline, manufacturing issues became salient concerns for Hybritech's executive posse. Greene and Adams put out the word to begin gearing and tooling. So, early in 1981, in anticipation of FDA approval of the IgE test, and with assistance from Bob Wang, Jeanne Dunham's small

manufacturing group started to expand and prepare for the mass production of diagnostic kits. The group's objective was to scale up the process that its counterparts in development were engineering. They needed to be able to manufacture assay devices in large quantities, efficiently and reliably, with a minimum of waste and error, and in accordance with established FDA standards – the agency's code of 'good manufacturing practices' (GMP) – for biologics. The company knew that samples drawn from manufactured lots would have to perform within the technical parameters advertised by the company and stipulated by the FDA as a condition of the product approval. The company also knew that achieving the necessary precision and consistency in product specs would be a complex technical and organizational feat. A year earlier, Greene had brought in Tom Adams as a vice-president to organize the firm's scientists and its development program. Now, to oversee the design and implementation of the new manufacturing operation, he decided to bring in another vice-president with experience in the large scale industrial production of biomedical products. Jeanne Dunham had done a fine job of packaging and shipping the research antibodies, but the task ahead was much bigger, far more complicated, and beyond the range of her expertise. Greene recalls, "We were looking for a guy to run manufacturing who was not just a manufacturing guy. This technology was very difficult, these biologicals."

Greene retained a headhunter named Mary Bowman to conduct the search. She came up with "this guy at Allergan, a superstar." Allergan was a large opthalmics manufacturer located in Orange County. The superstar's name was Ron Taylor. At just thirty-three years of age, he had already spent two years in Canada and two years

in Ireland establishing multi-million dollar manufacturing plants for the company. In reward for this stellar service, he was handed responsibility for all of Allergan's manufacturing operations, worldwide, including the U.S. Shortly after this promotion, however, Allergan was acquired by Smith Kline, and while Taylor "had a good job and was making good money," he began to think about leaving. After the merger, he says, "I went from being a member of the executive committee of a publicly traded, independent company to being a subsidiary manager, and it wasn't so much fun anymore." At first, representatives from Bowman's agency had trouble getting through to speak to Taylor, and he wasn't returning their calls. But, according to Greene, Bowman was determined to get her man: "Mary got on the phone, called Taylor's secretary, and said, 'This is Mary Bowman and I want his body. You tell him. I want his body.' And Ron was sufficiently intrigued to call her back."

Greene invited Taylor to San Diego for an informal talk over dinner, with Adams and Birndorf in attendance, too. He also brought the venture capitalists down from San Francisco to meet with the candidate. Brook Byers and Tom Perkins opined that Taylor had nothing to lose by taking a chance on the start-up. If Hybritech were to fail, they maintained, it would be because the risky technology wasn't ready for commercialization – in the event, it wouldn't reflect poorly on him. Taylor reports that they promised to look after him: "They said, 'Look, we're investing in start-up companies all the time, and if this one doesn't work, we'll find a place for you." The venture capitalists' arguments and assurances were convincing, and Taylor was absorbed into the network.

When he showed up for his first day on the job, in March 1981, he felt that he was starting from scratch. He didn't consider the company's packaging trailer to be an authentic manufacturing facility. Hybritech, he asserts, had "no facilities, no manufacturing, but they were getting close to filing some of the diagnostics products with the FDA." Nevertheless, while Taylor portrays the enterprise as primitive and inchoate, his view of the place illustrates how much it had changed in less than three years. Tom Adams says that, at Hybritech, he found "Ted and a bunch of scientists." Taylor characterizes the group that he joined in 1981 as "a bunch of guys that had been with companies." He adds that the presence of individuals with experience in business made the opportunity attractive:

> You had Tom Adams, who had worked at Baxter. Ted Greene had been at Baxter. There was a guy there who had been at Johnson & Johnson, Paul Rosinack. So, you had guys who had experience in big companies, who seemed to know what they were doing, and here they were off to create their own empire. So, it looked like a good thing to be a part of.[3]

By the time Taylor appeared on the scene, there was a management cadre in place, and the company was focused on commercial goals. The scientists were in the labs making discoveries – they were learning what could be done with hybridoma technology – but their inquiries were conducted in the service of product development, and there was certainly no academic precedent for the operational tasks that Taylor was hired to take on. He was recruited to direct an industrial unit, to build a manufacturing plant, to monitor quality control, manage materials in mass quantities,

---

[3] Taylor reports that he was in regular communication with Greene, and Adams, about technical issues related to the transfer of projects from the R&D program, Jim Jungwirth, Hybritech's first CFO, regarding equipment purchases, and Paul Rosinack and Cole Owen in marketing, about packaging.

and ensure regulatory compliance. The first item on Taylor's agenda was real estate. He needed to find a suitable site for the new operation. The space in the trailers was sufficient for the production of research antibodies, but manufacturing diagnostic kits was a far more elaborate undertaking. The company leased a warehouse facility, an empty shell, located about five miles to the east, on Carroll Canyon Road in the Mira Mesa section of San Diego's northern suburbs. The site was close to the Miramar Naval Air Station, in a commercial zone populated by a number of industrial parks. Taylor started staffing the operation and filling the shell with equipment and supplies. In many ways, the new place was a typical small production facility.

At the same time, however, the kind of manufacturing process that Hybritech was preparing to implement was unlike any existing operation in the diagnostics industry. In one sense, the objective was conventional. Hybritech was going to make diagnostic products under the watchful eye of the FDA, and Taylor was hired for his expertise in standard industry practices. But in another sense, the company's plans constituted a departure from industry norms. No commercial firms knew how to make diagnostic products with hybridoma technology. As Taylor explains, while the company's production processes were situated downstream from the research and development labs, setting them up still required expertise in cutting-edge science – at Hybritech, even the manufacturing operation took shape as a hybrid mix of academic and industrial influences:

> It was very, very highly technical stuff. You know, at Allergan, I'd been making sterile products for the eye, and that has its own set of technical issues, but boy, this biotech stuff was a whole different animal. In my part of the operation, I had probably a half dozen Ph.D.

> biochemists working for me in manufacturing. It was very complex. It wasn't simply a bunch of minimum-wage blue collar workers.

The work was distinguished from conventional antibody production because it was accomplished with hybridoma technology, and it was distinguished from conventional practice in the pharmaceutical industry because so much of it was based on biology rather than chemistry. Naturally, because the process lacked a clear precedent, and because it was so complex, many unanticipated difficulties arose as the process was organized. Just three years earlier, Royston and Birndorf had been among the first small group of academic researchers to employ hybridoma techniques. It was still a new technology. It hadn't been perfected or standardized, and nobody was certain about best practices for making antibodies with it, let alone making diagnostic kits with it. Taylor says:

> It wasn't like mixing two things together and ending up with a simple answer. You're growing things. They don't always grow the same. So, there were a lot of technical issues, just pure science issues that caused us trouble.... There wasn't fifty years of history that said, 'well, we know that this chemical has to do that.' This was all brand new stuff.

This posed a dilemma for the FDA – what standards were properly applied to evaluate this sort of activity? By 1981, a few commercial reagent suppliers had started making monoclonal antibodies. In diagnostics, however, only Hybritech had come up with an actual test that could be used in clinical laboratories (Centocor in Philadelphia and Genetic Systems in Seattle, two other tiny firms founded by academics, were following closely behind). Nobody had yet scaled up a system to manufacture products with hybridoma technology. Hybritech was the first, and so, the company ended up writing the authoritative book on the subject. Just as Hybritech had taught

the FDA about monoclonal antibody-based immunoassays early in 1981, so did it, later in the year, teach the regulators about good manufacturing practices with hybridoma technology. Taylor relates the circumstances:

> In a brand new field like this, where we were literally creating new science, we had to educate the Food and Drug Administration. They came in and spent weeks and weeks and weeks with us. In their normal routine it would be, 'we're here to audit your processes to make sure you're doing things right.' They were there trying to figure out what we were doing. They couldn't sort of write us up and say, 'Well, you've got a problem here.' They had nothing to base it on. The Food and Drug Administration did a lot of their groundwork with us, in how they would regulate these sorts of processes in the future.

In all of this, Taylor worked closely with Jeanne Dunham and Bob Wang. In October 1980, Russ Saunders had assigned Wang the responsibility of transferring new products from the development labs into manufacturing – conceptually, at least, for the company didn't yet have a facility equipped to assemble diagnostic kits. Wang was expected to design a scaleable process and provide manufacturing personnel with all of the necessary documentation. He hired a small group to assist him. As the team began exploring its options, it became apparent that it was going to be a trial-and-error affair. Wang says:

> When you're creating something, and you don't have a template to follow, then, you know, you're kind of guessing along the way. You have to do it somewhat empirically, and you know, some of the things that you put in there, you find that, 'Oh, this isn't really necessary.' Or you find that it may not be necessary from a practical standpoint, but it may be necessary from a regulatory point of view. So, there's a lot of balancing that you go through. We had a lot of revisions of documents, and the process.

It wasn't possible to rely on tried and true methods to solve problems, because, in many instances, there weren't any. Many of the problems had never been

encountered before, anywhere. Wang's team adopted an experimental approach. The job called for flexible strategies, and a boss who was willing to tolerate and even encourage some creative improvisation. As it turned out, Ron Taylor was perfectly suited to the job. Wang has no complaints about working with him. He says, "Ron Taylor just more or less let me do what I wanted." Taylor understood the kind of environment in which he was operating. He recognized that the system was going to perturbed by unexpected happenings, and that the kind of control over the process that might be expected in other manufacturing contexts was not likely to be managed at Hybritech, at least initially: "We found that specifications for results – how should something work – were very, very difficult to pin down." He adopted a managerial style appropriate to the circumstances. Ted Greene gives him credit for it:

> Ron is not a hierarchically structured guy, and he doesn't run manufacturing by the books. He delegated a lot. I think that was absolutely critical because you couldn't write down all these recipes and procedures because they didn't really exist. And every time you'd make a batch of reagents, they'd be different. So you have to have really clever people, motivated to figure out how to do it, and how to make it work. I think Ron did a spectacular job at that.

BIG VATS OF ACID AND BIG LOADS OF MICE

Certain aspects of the process took the company's biochemists on adventures into remote and entirely foreign areas of industrial production. Scaling up the chemical etching process used to prepare the solid phase substrate proved especially challenging, and the incubation of hybridomas and the production of monoclonals in large quantities turned out to be difficult to manage, as well. These tasks were central to the company's commercial objectives, but no one at the firm, or anywhere else, for that matter, possessed relevant prior experience with them because they hadn't been

attempted before. The company had made and sold some antibodies, and the assay chemistries had been devised, but, in terms of Hybritech's grand commercial scheme, those accomplishments were only tentative beginnings. Jeanne Dunham summarizes the scale-up dilemma: "It's one thing to do it in a beaker, but then to try to do it in huge quantities, it was difficult."

The amination of the beads used in the TANDEM kits – that is, the formation of amino acid groups on the polystyrene – was a critical step. It 'activated' the surface of the styrene for covalent bonding with the 'capture' antibodies. The process included successive, timed baths in sulfuric acid, nitric acid, and, finally, a solution of stannous chloride in hydrochloric acid. When Wang devised the solid phase chemistry, he had been working with about a dozen beads at a time. Now, he had to come up with a way to aminate beads in batches of eighty or ninety thousand – enough to fill a vessel with a volume of one hundred liters. To perform this task, the company designed a special room that contained, installed in the floor, large open vats and drainage canals for the acids. The room also a housed a robotic transport system that lowered containers filled with several hundred pounds of beads into the acid tanks before lifting them back out again and conveying them to a rinse or to the next bath. It was a tricky process, and, Saunders says, "It was dangerous....I remember a fellow named Gary Jones being covered in rubber. That's how we made the active beads." The process was also expensive. Even the containers that held the beads were costly. Only high-grade, corrosion resistant stainless steel could be used. "It costs a lot," Wang states "to purchase stainless steel containers that large."

Certain aspects of the amination process were never completely mastered. Dunham recalls some of the questions that arose: "Do you stir the beads? Do you not stir the beads? Do you just dump them?" The manufacturing team had to experiment in order to find out, but it didn't usually have opportunities to optimize its methods. Bob Wang recalls wrestling with many practical questions that remained largely unanswered – for instance, "What do you do with the acids after you're done?" Apparently, the company never had time to complete its education on the topic:

> We never figured out, 'Can you reuse the acids?' Eventually, in later years, I did some experiments to show that if you look at the mole equivalents that were being consumed, you know, by the chemical reactions that were going on, you could reuse the acids a lot of times. And we started reusing the acids two or three times, but people didn't want to take the chance of using them more often than that. We started to see some changes. So, we did start to reuse, but disposal of the acids afterwards was a real challenge.

Looking back, Wang admits that, "We didn't put a real good effort into making the system as robust and high quality as we could have. We didn't have time to go back and improve it." Nevertheless, despite the embedded flaws and inefficiencies, the original bead treatment procedures became the backbone of Hybritech's TANDEM assay production scheme. "Even after I left Hybritech in 1986," Wang says, "They were still using that same chemistry, the same process I developed.

Other manufacturing difficulties had to do with the procurement of materials. Identifying the appropriate kind of bead – one made of the right sort of polystyrene and featuring a surface roughness suitable to the company's purposes – was difficult, as it turned out. A good deal of experimentation was required. And once the company's researchers had determined which characteristics were best, the firm was

unable to locate a dependable source. According to Dunham, Hybritech originally did business with "a guy in the Midwest, one of these shady character type guys, who sold the beads, who wasn't very reliable." The company was eventually able to negotiate contracts with a number of different suppliers, but early on, Dunham says, "We were constantly searching for another source of beads. There was only that one source."

Making antibodies in large quantities also posed serious procurement problems for the manufacturing group. Hybridomas were incubated in mice and monoclonal antibodies were harvested from extracted ascites fluid. The animals were efficient producers of antibody, but this was not a clean or scaleable method. Dunham asks, rhetorically: "How do you scale up mice?" Eventually, commercial monoclonal antibody producers began adapting large scale, in vitro cell culture methods that employed fermenters and bioreactors of various sorts, but maintaining living cells is a recondite art, and finding the right conditions for hybridomas was a complicated, time-consuming process. In the beginning, when Hybritech was rushing to get its first products out on the market, the firm's manufacturing personnel didn't have time to conduct experiments on new methods for culturing cells. So, the company's solution was simply to get more mice. As kit production expanded, handling the animals became a massive chore, and the company had to construct a huge vivarium. Ron Taylor recalls:

> We got to the point where we were processing twenty to thirty thousand mice a month, and we had quite a staff that took care of them. I mean, it's pretty gruesome, but the animal rights people, they had no idea where we were. We had a building that was absolutely unmarked – no markings on it at all. You couldn't tell what was going on in there. That was our little antibody factory, where we were hauling in live mice and hauling out carcasses, twenty or thirty thousand a month.

Maintaining a supply of mice sufficient to keep the company in antibodies turned out to be a constant struggle. Hybritech was purchasing its animals from Charles River Laboratories in Boston, along with a couple of other suppliers. Charles River is today a huge, publicly-traded corporation. It employs about 7,500 people, and its annual revenues presently hover around the $1 billion mark. It sells numerous strains of rats and mice, and various other 'experimental models' to scientific customers around the world, and it conducts its own research on the genomes of the species (and 'trans' species) that it produces. The company's website announces that, "We are a global provider of solutions that advance the drug discovery and development process."[4] Jeanne Dunham claims that "Charles River was able to grow to the size that they are now because they were able to offer us all of these mice." Hybridoma technology represented a boon to laboratory animal vendors. Before Hybritech, no organization of any kind had employed mice in such quantities. Dunham relates that, initially, only Charles River could come close to meeting the demand, but that shipping the animals across the country from Boston to San Diego was a problem. It resulted in significant losses. At Hybritech, employees would often open up boxes to find most of the animals dead: "They're cannibals, you know, so if they don't have enough water or they don't have enough food in transit, then you'll open up the box and there will be only one or two mice left. And tails. They eat everything except the head and the tail. All gone. So, that was our biggest problem."

[4] Go to http://www.criver.com.

Hybritech employees crafted a number of inventive methods for dealing with the large numbers of mice in the operation. Jeff Janus, for example, a UCSD graduate that Dunham hired as a technician in the vivarium, developed a novel instrument for 'processing' mice after removing ascites fluid from their peritoneal cavities. Janus became very efficient at collecting the fluid, but he didn't derive any satisfaction from the job because, afterwards, the mice had to be killed. He was especially troubled by the methods available for disposing of the animals (bludgeoning, drowning, suffocating, etc.), so he devoted some time to experimenting with alternative techniques. Dunham reports that he eventually came up a device that pleased him, and he began using it. Compared to other means of dispatching mice, Janus' method was relatively inefficient, so this was a piece of proprietary technology that the company declined to patent, but Janus preferred it nonetheless:

> Jeff made an actual mouse guillotine. He had this plexiglass piece that was on an angle, and the little mouse was just spread-eagled on there, and you held down the little legs with little clamps, and then....So, it got...I mean, don't tell your animal activists friends about this thing, but it was humane. I mean, he was trying to come up with a humane way of sacrificing these mice, and not having them suffer.

Hybritech's manufacturing operation broke new ground in many ways, and, for the most part, it was, like Janus' guillotine, constructed on the fly in response to emergent problems rather than modeled after some grand design, or built according to some set of theoretical principles. It was hastily assembled within a firm that was simultaneously trying to orchestrate processes of technological innovation and organizational expansion in a competitive market environment. From the beginning, there were problems with quality control. The technology was sophisticated and

complex. It didn't lend itself to rapid commercialization and scaling. And, in certain respects, as Greg Payne, a technician in the firm's R&D unit, describes, manufacturing was an afterthought for the organization.[5] The scale up process was often a painful one:

> In the early days, it was very much an R&D driven company. R&D had a lot of power, and we would essentially do all of the [regulatory] submission work, and all of the testing on R&D lots. And I'm not saying it derogatorily, but we would shove it over the wall to manufacturing, and they would sink or swim. You know, it was a small company and a lot of the necessary processes weren't in place. We just didn't know. And we ended up in situations where we manufactured product that really didn't meet the same performance specs and claims as the ones that were developed in research. So we had to work that out. I think it was a big challenge for us to transition from a research organization to actually making product.

Taylor recalls many disputes with the R&D group, and with the sales and marketing group, as well. Both groups wanted improvements in product quality, and in the reproducibility of lots. The developers would regularly insist that the company's kits simply had to perform within certain specified technical parameters. Taylor remembers R&D people declaring that, should a product fail to meet the specs, then "'the test isn't going to work.'" But manufacturing would often find, and argue, that while it was impossible to make products the way R&D demanded, the tests did, in fact, work, after all. Consequently, Taylor says:

> We were shipping product out frequently that failed our own specifications, but that we knew, fundamentally, worked just fine. I

---

[5] In a business school study, Gary Pisano questions what he calls the "prevailing wisdom" regarding R&D driven industries like pharmaceuticals. According to Pisano, it is widely believed (by business scholars and businesspersons alike) that "...where new product introductions are the name of the game, process development and manufacturing competence are of secondary importance." Against this notion, Pisano argues that there is "hidden" strategic leverage for firms to tap in process development capabilities. See Gary Pisano, The Development Factory: Unlocking the Potential of Process Innovation, Boston, MA: Harvard Business School Press, 1997; p. 19.

> couldn't get the R&D guys to change the specs, because you can't just arbitrarily change the specs. You've got to get the R&D guy to agree. So we had a lot of battles that way. Instead of simply back-ordering a product, we'd say, 'No, this is good enough to ship. We're going to ship it with a variance that says it didn't meet this specification.'

One organizational tactic that Taylor employed to alleviate tensions between R&D and manufacturing was to recruit personnel from R&D to help scale up production processes: "I basically said, 'Look, if you guys are going to be such critics over there, come over on my side and see what happens.' And sure enough, once they became part of the manufacturing operation, the process of improving process development, all of a sudden their eyes opened up to the real world problems. So, it helped." Of course, the sales and marketing people never got comfortable with the idea of shipping products with labeled caveats regarding performance specifications – the cautions meant that they would likely have to deal with customers' questions, or worse, silent assumptions regarding the quality of the goods. It was fine for the manufacturing unit to deny that variances made for 'inferior' products, but it was up to sales and marketing folk to persuade or reassure customers. Bob Wang suggests that there is no remedy for conflicts between marketing and manufacturing departments: "You know, marketing wants the products to be a panacea for every ill in the world. Marketing wants manufacturing to have perfect products made every time, and now, not late. Same old stuff."

Somehow, it all worked. The company put its products on the market, and they sold. All of Hybritech's diagnostics kits were well received by clinical laboratories when introduced. Incorporating monoclonal antibodies into the TANDEM assay format enabled Hybritech to offer tests that were just as accurate as

those manufactured by the competition, while featuring greater speed, sensitivity, and ease of use, at comparable prices – even if the kits didn't always perform up to the targeted specs. So, despite all of the uncertainties and problems that the company had run into along the way, it had successfully commercialized hybridoma technology. And the revenues that were generated were important, not just because they helped the firm to pay some bills, but because they validated the technology. The company acquired a halo, and raised money on the radiance. It conducted further research, developed new products, and continued to get bigger. Hybritech was a pioneer in its field. It was the first, and it tried to promote and capitalize on the notion that it was the best, too.

In its early days, Hybritech had resembled nothing so much as an academic laboratory, but, by the end of 1981, it had become something very different. The firm still housed scientists who conducted cutting-edge research, but it had also integrated structures and functions that academic laboratories never acquire – commercial products, a large manufacturing operation, and a sales force, for example.[6] By the end of 1981, Hybritech was distinguished from an academic laboratory by more than just the fact that it happened to maintain a profit and loss statement. It had become a full-fledged diagnostics company. But it was still unique. The mix of people and practices that constituted the firm were unlike those found anywhere else in the industry.

---

[6] The company was also working to build an international distribution network for its products. In August 1981, Hybritech established a subsidiary in Belgium to initiate sales in European markets. Guy Van de Winkel and Michel DeCoux, both former Baxter employees, were named vice-presidents. A U.S. subsidiary of Boehringer Mannheim had been contracted to distribute Hybritech's research antibodies in domestic markets, and Mitsubishi Chemical Industries, Ltd. had been granted exclusive rights to sell the company's in vitro products in Japan. See Hybritech, Inc., "Initial Public Stock Offering Prospectus," October 28, 1981.

GROWING PAINS

The social sciences have long recognized that the size of a group or organization influences the character of its constitutive relations and interactions. 'Progress' in the Western world has been accompanied by population growth, the formation of large cities and states, and the rise of complex social organizations. So, naturally, since the social sciences first began trying to explain the confusing processes of modernization, industrialization, and urbanization in the late 19th century, practitioners have devoted attention to the significance of numbers in social life. Their studies of numbers have led them to paradoxical conclusions. Georg Simmel, for instance, examined the quantitative aspects of groups and found that the dynamics of relationships or interactions between two people (dyads) are very different than the dynamics of relationships or interactions among three (triads).[7] The presence of the third modifies circumstances and introduces new social possibilities – impartiality, mediation, and domination by numbers, for instance. Simmel also observed that as group size increases, different forms of association come to predominate. Small groups are characterized by familiar, informal relations; larger ones are characterized by impersonality and formalized relations. Life in a village where there are few is different than life in a modern metropolis where there are many. The village is homogeneous; the city is differentiated. The village offers few choices; the city encourages individuality. Village life tends to be stable, predictable, and sedate; city

[7] Georg Simmel, "Group Expansion and the Development of Individuality," pp. 251-293 in On Individuality and Social Forms: Selected Writings, ed. Donald N. Levine, Chicago: University of Chicago Press, 1971.

life is vibrant, uncertain, and stimulating.[8] The paradox for Simmel was that, as numbers, social distances, and personal freedoms increase, so do the abstract, 'objective' powers of society over the individual.[9] And against the force of numbers, he saw, individuals can summon only apathy and detached indifference. Cities are intense, but their denizens cool.

Max Weber found a similarly unsettling denouement in the increasing complexity and size of modern social orders and institutions.[10] He attributed the rise of capitalism, the rule of law, and bureaucratic administration – the hallmarks of modernity – largely to the concomitant ascendance of instrumental rationality as a basic organizing principle and a dominant element of consciousness in modern social life. Weber saw that where an organization is designed for the efficient pursuit of a given goal or value, it will, in the routine course of business, tend to lose sight of its mission, and become concerned, first of all, with the perpetuation of its own hierarchical structure. Standardization and regimentation typically prevail, and to the extent that organizational environments become rule bound in this manner, conformity is expected, creativity is discouraged, and innovation is stifled. For persons who remain committed to the stated goals or values of thoroughly rationalized organizations, participation loses its meaning and its sense. The paradox for Weber

---

[8] Georg Simmel, "The Metropolis and Mental Life," pp. 409-424 in The Sociology of Georg Simmel, trans. Kurt Wolff, New York: Free Press, 1950.

[9] Georg Simmel, The Philosophy of Money, 3rd ed., David Frisby; trans. Tom Bottomore, from a first draft by Kaethe Mengelberg, London: Routledge, 2004.

[10] Max Weber, Economy and Society, eds. Guenther Roth and Claus Wittich, Berkeley, CA: University of California Press, 1978.

was that reason for large numbers leads to its antithesis for the individual. Large scale, complex social organizations are disenchanting.

The sociological insights of Simmel and Weber are, of course, available to any competent participants in modern social life. People regularly discover that 'two's company, three's a crowd,' and that more are 'madding.' They often report feeling 'like a number,' or being 'caught in red tape.' Like social scientists, they have experiences in the world and they sometimes draw theoretical conclusions about them. At Hybritech, members of the organization observed it change and grow over time, and they commented on it. Those who were present at the beginning witnessed numerous transformations within the firm during its first few years. The changes came with dizzying rapidity. From Hybritech's inception in 1978 through its sale to Eli Lilly in 1986, the company never settled into a rhythm or a stable pattern of development. It wasn't like a steam engine gradually working up momentum and then chugging along at a measured pace. It was more like a rocket hurtling through the stratosphere, attempting to escape the pull of gravity. Its growth was uncontrolled. In its career as an independent producer of diagnostic products and a pharmaceutical R&D operation, Hybritech was buffeted by forces of disruptive change that emanated from both internal and external sources. As the business grew from a tiny start-up to a large manufacturer, its circumstances and characteristics were altered dramatically. Participants in the process have told stories about it.

Hybritech's revenues climbed steeply through the entire first half of the 1980s. By the end of 1982, the company had seven TANDEM products on the market, and all of them were gathering significant market shares. The company claimed more than

900 clinical laboratory customers in the U.S., and its European and Japanese distributors had initiated product launches. The firm had also established an R&D arm dedicated to work on assay instrumentation. Hybritech had decided to get into the hardware business.[11] By the end of 1983, the company had introduced the TANDEM-E series, and the FDA had cleared seventeen of its diagnostic products for sale. The firm had introduced its own semi-automated immunoassay analyzer, called the PHOTON, and it claimed to have over 1,700 U.S. customers purchasing its diagnostics products. In October 1983, Hybritech announced that, in the previous three months its revenues had exceeded its operating expenses. The company had realized its first profitable quarter.[12] In 1984, Hybritech reported total operating costs of $32.7 million (nearly $14 million funded R&D) and revenues totaling $30.8 million ($14.6 million from product sales and $16.2 million from contract revenues). The company still managed to claim a small profit of $1 million for the year when additional interest income was factored in.[13] The enterprise was enjoying success. The diagnostics business was very healthy, evidently, and the company was managing to cover the enormous sums required to fund R&D on imaging and therapeutic

[11] The decision to get into instrumentation was controversial around Hybritech's executive offices and in the boardroom. Some in the company believed that, given customer demand, any diagnostics manufacturer without its own automated instruments would soon be cut out of the market. Others disagreed and wanted to focus resources on product and service improvements in other areas. Although dubious about it, Greene eventually opted for instrumentation.

[12] Hybritech, Inc., "1982 Annual Report," May 11, 1983.

[13] Hybritech, Inc., "1984 Annual Report," April 29, 1985. Contract revenues were received from other commercial firms for work performed in cooperative R&D partnerships, or research on custom antibodies; from the government for supplying conjugated antibodies for clinical investigations; and from limited partnerships in which the company assigned to investors, not ownership shares in the company, but property rights on products of research conducted in the company's laboratories.

products. (Gary David had initiated experimental work in these areas late in 1981 after the first TANDEM kits had been introduced).

The company had grown immensely in a very short period. By the end of 1983, 300 people were employed at Hybritech. When the clock ran down on 1984, the total had surpassed 500. And, according to Bill Crean, who joined Hybritech in 1984 as director of human resources, the figure topped out, just prior to the sale of the company to Eli Lilly in March of 1986, at somewhere between 1,100 and 1,200.[14] This company hardly resembled the little start-up of just a few years earlier. Hybritech had moved its labs and offices out of the La Jolla Cancer Research Foundation, and the trailers, early in 1982, into a new building of its own. Ted Greene recalls how, at the time, the size of the company's regular 'all employee' meetings kept increasing until they eventually became unmanageable in the company's tiny space at the LJCF: "We used to have monthly meetings that got bigger, and bigger, and bigger. Finally, we had to go to the new building because, you know, we were renting space everywhere. God, we were building. I remember at one point we had to rent chairs." The new company headquarters were located on Torreyana Road, just down the street, still very close to UCSD, Scripps, and the Salk. The new structure was emblematic of changes that were taking place inside the company. Hybritech's executives saw the move as an opportunity to work on the firm's corporate image. When the construction of the new building was in the planning stages, the architectural façade became an important matter for executive committees to weigh.

---

[14] In 1985, Inc. magazine ranked Hybritech Inc. as the 10th fastest growing publicly held company in the United States over the previous five years. According to Inc.'s calculations, Hybritech displayed an annual growth rate of 212% during that period.

They approved a fashionable, sleek exterior befitting a young high-tech company on the rise.

Walt Desmond remembers that the impressive new space had palpable effects on Hybritech's organizational culture: "It just instantly had a more corporate feel, which the science people didn't necessarily appreciate, but obviously was essential. You know, the appearance and the address, and sort of the amenities, and so forth, are what you have to have." Desmond tells a story about the building on Torreyana that illustrates Ted Greene's approach to promoting Hybritech. The new headquarters were perched high atop Torrey Pines Mesa, a narrow coastal plateau situated between the Pacific Ocean to the west and the Sorrento Valley to the east. The building was constructed on the east rim of the mesa, at the edge of a cliff, alongside Torrey Pines State Reserve, one of the last homes in the world to Pinus torreyana, an ancient conifer that survives today only on this tiny piece of coast between Del Mar and La Jolla, near San Diego, and on Santa Rosa Island, one of Southern California's Channel Islands, off the coast of Santa Barbara. Originally, the new building had been painted in muted tones, but Greene immediately ordered that it be repainted a bright white so as to be visible from Interstate 5, the principal link between Los Angeles and San Diego, which runs through the Sorrento Valley far below. The company employed bright people, and it was making smart progress. Greene considered it appropriate that Hybritech's new home should beam. Desmond describes the location:

> It's right up on the edge of the sagebrush. In fact, it encroaches on Torrey Pines State Reserve, where I'm a docent. When they built the building, it was gray, and one of the things that Ted Greene wanted to do was get that thing white as soon as possible. The architect picked this specific gray, you know, sagebrush, to blend in with the

> environment, and all of a sudden, it's given this sort of Taj Mahal white that sort of jumps out at you from the freeway.

By outward appearances, Hybritech was humming along efficiently, comfortably ahead of its competition. Inside Greene's San Diego mahal, however, activities sometimes teetered on the brink of chaos. Initially, Hybritech was nearly overwhelmed by the numbers it had to absorb, and, in certain respects, the executives directing the firm never really caught up with the ceaseless expansion. In 1981, when Hybritech's growth spurt began, the company had no human resources department to 'in-process' new employees. It fell to the managers already on hand to deal with the steady stream of people walking in the door, in addition to their other duties. Interviewing job candidates sometimes entailed significant after-hours time commitments. Cole Owen, who, during this period, was busy trying to complete various marketing projects against impossible deadlines, recalls that he and others dedicated evenings to recruiting chores:

> I don't know how many people a month we were interviewing. I interviewed the first CFO, R&D people, manufacturing people, and, of course, marketing people. There were three or four of us who were routinely involved in just sort of being in the circuit to help get an impression, sort of screening and reading. We'd go to dinner with people. I must have gone to dinner twice a week, some weeks, with candidates. One time it would be someone from one group that would ask you, 'Would you meet with them?' and another time, they'd be from another area. And you know, I'd do the same thing. I'd be talking to someone, and I might have Russ Saunders from R&D spend time with them, just to help. We didn't have a personnel department.

Finding good help was a problem as the company grew, especially in manufacturing. Hybritech's diagnostics business was expanding so quickly and the pressure to produce kits was so great that the manufacturing group was forced to hire a

largely unskilled labor force. Many of the recruits were new college graduates, fresh from UCSD's chemistry and biology departments, but Jeanne Dunham asserts that, despite undergraduate training in the sciences, these people were still generally unprepared for the work at Hybritech:

> Someone directly out of UCSD is not a qualified person. They had a basic understanding of chemistry, but they weren't teaching that in a way that you could then go out into the world and use it. I mean, everybody who came into the facility, you had to train, every single one of them. They maybe knew the basics – this is a ph meter, yes, yes – but none of them had GMP experience, not one of them. So, we had a lot of training classes.

Greg Payne remembers chemistry and biology majors as among the candidates with the best qualifications. He claims that manufacturing was grabbing as many bodies as it could, wherever it could get them, and "it didn't matter if you had a science background or not." The influx of untrained, under-trained, or poorly trained persons changed the character of the place. It further destabilized the already improvisational and sometimes slapdash and make-do nature of process development at the firm. There was, as always and everywhere, a lot of learning on the job, but, at Hybritech in the early 1980s, where the work was scientific, impromptu courses were often elementary or remedial. In a company that had been populated at the beginning almost entirely by scientists from laboratories at world class research institutions, the new staffing effort introduced a good deal of social diversity. As the company grew, it became differentiated, naturally. Distinctions were made, communications became more difficult, and nerves sometimes frayed. For some of the 'old-timers,' it was frustrating. Payne's recollections still take the form of gripes: "We'd be working in development to write these manufacturing documents, but you know, you have to have

a little bit of knowledge of basic science, of basic techniques, before you can use them."

Growth and internal differentiation required the organization to adopt more formality in its routine practices. As the group got larger, the fund of useful shared experiences – Hybritech's 'organizational memory' – became more diffuse. When new members of an organization lack the common knowledge of the place and the justifications that make established procedures sensible, then they have to be taught. In high-tech start-up environments (as everywhere, but perhaps more so than in many other settings), training functions are balanced against constraints of time and money, and, in education, economy is not a virtue. When high rates of personnel turnover make apprenticeships impractical, or high rates of process innovation diminish their utility, then teaching and learning necessarily become formalized. Rules have to be articulated, so new members will have some guidelines for action. Organizations typically have interests in preserving practices that work, but they are also under pressure to expand and renovate, and that hinders conservation. As far as organizational habits are concerned, progress and persistence are antithetical. The idea of managing innovation is incoherent (if management implies direction or control of some sort).[15] When people come and go, and when they devise and implement new methods of production, they introduce organizational discontinuities. Bob Wang suggests that, within social and technical systems, change creates social distances, and

[15] A zen approach could be formulated, I suppose (and some business guru has almost certainly already done it). The way to manage innovation is to leave people alone and let them do their thing. Strictly speaking, companies don't innovate, people do. Some companies let them, others don't, and many are in the middle, unfettering or interfering to varying degrees.

social distances create knowledge gaps that have to be filled or crossed if practices are to be sustained.[16] It's a problem:

> You want to get people to understand what the mechanisms are for getting things accomplished, the systems involved. You know, you evolve systems for specific reasons. And you want to make sure that people follow those systems and understand why you're doing what you're doing as opposed to just doing it, and then later on saying, 'Oh it would be easier if we did this,' because when that happens, then you're essentially negating the reason why you've developed the system in the first place. I mean, eventually, you lose a lot of the history and understanding, that knowledge base, when people move on. You try to disseminate, as much as possible, the logic behind the things that you're doing.

When funds of practical knowledge and experience are thin, or, perhaps, cannot be readily tapped, explicit rules may be formulated, as a last resort, in order to close gaps in organizational memories. The wider the chasm, the more has to be made explicit. Greg Payne gives a concrete example. He describes how he and his colleagues went about teaching Hybritech's manufacturing novices some of the steps for purifying monoclonal antibodies from ascites fluid, a process that, apparently, didn't go so well on at least one occasion, and probably more:

> We would say in our documents, 'dialyze the antibody,' which meant the antibody solution which we had precipitated via high salt concentrations. You would put it in a bag, a semi-permeable membrane, and all the low molecular weight salts would dialyze out, go out through that membrane, and essentially what you'd end up doing over time, over multiple changes of this buffer, you would end up lowering the salt concentration. Well, I think anybody that knew any science at all would know that when you did that, you had to put a magnetic stir bar at the bottom, and that you had to have good mixing in order to get efficient dialysis. Well, all of a sudden, we're working on these documents, and they'd say, 'Well, it didn't say stirring so we didn't stir.' Well, you know, what happened to your common sense? What happened to your basic knowledge? All of a sudden then, these

[16] For a scholarly discussion of these issues, see John Seely Brown and Paul Duguid, The Social Life of Information, Boston, MA: Harvard Business School Press, 2001; ch. 4-5.

> documents, because of this philosophy in operations that anybody could come in, had to be really specific. We had to say 'with stirring,' and so on.

A lot had to be formally articulated, and that made for cumbersome operations at least initially. Fundamentally, the problem did not have to do with a lack of scientific knowledge. It is better understood in social terms. It was a problem of numbers, of size and social differentiation. There were people in the organization who knew all about dialysis. The problem was communicating this knowledge to other affiliates who needed to possess it. And the unskilled novices who were ignorant about salt concentrations and magnetic stir bars weren't the only ones with things to learn before the manufacturing operation could run smoothly. As Payne points out, the scientists in development were also ill-prepared for their jobs. They needed to become better informed about manufacturing standards and practices. The development researchers didn't have to break out chemistry textbooks in order to learn about dialysis, but they flunked a few quizzes in manufacturing 101, and were required to study the 21 CFR 820, the pertinent section of the FDA's code of 'good manufacturing practices' (GMP). Of the social distance between science and manufacturing, Payne says:

> I think that there were a lot of things that the development people had to go through in learning about what it takes to make products under Good Manufacturing Practices. You had to document things very well. You had to have somebody verify it, you had to follow established procedure. It was a little tough for some of the people in development.

So, the problem, at bottom, wasn't the absence of any particular bit of technical knowledge or information, but rather a lack of organizational know-how and coordination. The relevant sorts of experience were not distributed broadly enough

within the company. "The people at the company were very educated," Payne says, "but a lot of them, maybe they hadn't been around in the industry long enough to know a lot of these things." The condition was diagnosed, and then Hybritech formulated, in effect, a modern prescription for its modern ills. There were no philosophical deliberations on methods, of course, for Hybritech was in business, and the appropriate course of action was plain: the place needed to be rationalized. It needed to get bigger. The troubles in manufacturing would be alleviated when experts could be brought in to stabilize the operation. The experts did, then, come in, and they wrote up sets of rules. They rationalized the place. The rules satisfied the FDA, but in terms of transforming the company's manufacturing procedures, the scribbling hardly mattered. What mattered were numbers. Payne explains: "As time went by, we hired more and more people in from the outside that had some of this experience, and they had to develop the systems and put them in place." Payne talks about the trouble sociologically. "You know," he says, "there were growing pains."

MAKING FRIENDS AND STRANGERS

As Hybritech's numbers inflated, the sense of common purpose that animated the company in its early years started gradually to disappear. When the firm was small, relations among persons were close. Everyone employed by the company was together, physically co-present, in small spaces – the laboratories and the trailers at the La Jolla Cancer Research Foundation. The names and faces were all familiar. There were no strangers. No great social distances separated individuals or groups within the organization. In the early days, Ted Greene used to hold parties for the entire company – everyone employed by the firm was invited into his home as a guest. It

wasn't long before these kinds of gatherings became impossible. The parties didn't cease simply because Greene's house wasn't big enough to accommodate the growing numbers – at the same time, the notion of welcoming all became inapposite. Strangers started appearing at the company, people that Greene wouldn't invite into his home simply because he didn't know them. Cole Owen observed this change, and to talk about Hybritech's past, he articulates a general 'lay' theory of organizational numbers. Like Simmel, Owen notes that organizational dynamics are influenced by size. Hybritech's intimacy early on, he suggests, reflected a simple social geometry:

> I think an element of it is that when you're forty, fifty, or sixty people, nobody is that far from Ted, you know, the president, or whoever the president is. I don't care if you're receiving in the back, and signing off on something, 'Yeah, we got something from Scientific Products,' or if you're mixing buffers or washing glassware. The president knows who you are, your name, where you work, who you work for, what you're doing, and so, there's a closeness from that standpoint, and, at a couple of hundred people, you can't do that anymore. You start having to have an infrastructure, you have to have some leveling mechanisms because one person really can't effectively assist, support, manage, and supervise more than seven or eight, or ten people, twelve, maybe, and then that person's got to report to somebody and that person...so you start getting a hierarchy, and you just can't put it off beyond a couple of hundred people.

Owen goes on to explain exactly why it can't be put off. He cites physical limits that social systems are obliged to observe. If they're not heeded,

> ...then you have somebody at the top who's trying to micromanage everything and then they end up making decisions for the person in the warehouse in the back, whose supervisor then says, 'Well, we're going to do a blue one,' and then he says, 'No we're not. I already talked to Ted. We're going to do a red one.' And that's when the system starts to come apart sometimes. So, at a couple of hundred, you have to have that, and by the time you get to about five hundred, there really starts to have to be some distance between the most senior level person, or two or three people, and the people moving boxes in the back. I mean, they

> just don't have the proximity and the access to that person. Just mechanically, you can't do it anymore.

Greg Payne indicates that Hybritech's early lack of 'leveling mechanisms,' hierarchy, and reporting structures – and the coziness that characterized the company in their absence – was important to him, and to others, as well. It made Hybritech a desirable place to be:

> You know, in a big company, you'd never talk to the president or CEO. But there were times when you were in conversation with Ted, or there were times when we'd be in the cafeteria and they'd have food, and beer and wine and stuff, and Tom Adams would come up and ask me a question. He'd be talking to somebody else and come over and ask me a question. So you would interact with everybody in the company, and that really made it nice because you really got to know people.

As Payne tells it, there was a unique spirit in the company that derived, partly from the excitement of working with a novel, leading edge technology, and partly from the quality of social interactions within the close quarters of the firm: "There was a lot of camaraderie, and a lot of excitement about what we were doing. And Ted Greene was also pretty good about pumping up morale." In addition to displaying his natural exuberance and enthusiasm for science and technology, Greene worked deliberately to provide Hybritech employees at all levels with incentives and motivations that extended beyond wage or salary compensation, and, at the same time, with a sense of belonging. The company's stock program was an example. Greene saw to it personally that all employees were enrolled and given at least a small piece of the company. According to Owen, the stock plan "was driven by Ted. He made sure that every clerical person, dishwasher, secretary, receptionist, everybody, was in the program." It was important to Greene that everyone at Hybritech felt like they had

a stake in the enterprise. Whether everyone did, in fact, feel this way, or didn't, is another matter, but many at the company observed Greene making the effort, and it made an impression. It counted for something. Greene's individual efforts contributed significantly to the spirit and vitality of the place, and others made similar attempts.

The firm's scientific projects also served to bring people together and to generate feelings of unanimity, confederation, and pride. In the late 1970s and early 1980s, the field of hybridoma technology was exclusive territory – Hybritech was developing advanced scientific techniques possessed by few other corporate or academic entities. The company's research teams could reasonably claim to know as much about monoclonal antibodies as any other group on the planet. Participating in something so new, and potentially so important in the worlds of science, medicine, and commerce, meant a great deal to the company's researchers. They were excited about the technological opportunities. Hybritech's leadership in its field made the start-up a special place for life scientists to be. The scientists were also appreciative of the freedom in research that they were granted in the company's laboratories. At Hybritech, they could conduct experimental inquiries and explore technological possibilities free from teaching responsibilities, the burdens of grant-writing, and pressures to publish in academic markets that often seemed to lack means for distinguishing quality and quantity, and mechanisms for appropriately rewarding creativity and invention. At the time, for many at the firm, Hybritech seemed a better place to be than the academy. Gary David was responsible for much of this feeling. He set the tone in the company's labs. He was scientifically oriented – so much so

that, according to Bill Crean, "the more business-focused people could sometimes get impatient with him." And in his role as lab chief, David was roundly known, Crean says, as "a real nice guy, very laid back, easy to work with." In the beginning, thanks to David (and Ted Greene, too), scientific work at Hybritech was unencumbered. The atmosphere in the laboratories was a big part of the company's appeal. The scientists were generally happy to be there. Ted Greene, too, was happy to be there with them, so, early on, the positive vibes flowing through the place were contagious.

As Hybritech reached the point where it was ready to market its diagnostics products, having persons from every corner and all levels of the firm pitch in to help with manufacturing, packaging, and shipping was another means by which the firm cultivated organizational solidarity. The practice helped the company to achieve its production goals, but it also helped to create an atmosphere of cooperation and teamwork. Cole Owen says: "I sat in production lines on Saturdays for Jeanne Dunham. I think that was really important to confirm to the people in manufacturing that they weren't out there by themselves. When they needed extra pairs of hands, people from R&D, people from marketing, everybody got on the line and helped." Even as late as 1984, when Hybritech rushed to move its new ICON pregnancy test to market, scientists and managers stood on assembly lines to help the firm accomplish its scheduled goals. The company was operating under severe self-imposed time constraints because it was clear that the device would be a huge commercial success, and the company wanted to start making shipments before a particular date for accounting purposes. Requests went out to all employees to put in extra hours. David Hale, who had by that time joined Hybritech as the company's president and chief

operating officer (Greene had been titled CEO, and made chairman of the board), said of the ICON effort: "The R&D people worked their regular shift, then on operations as a second shift. Even top management worked on packaging to set an example."[17]

The early successes of the company followed strenuous collective efforts to conquer imposing technical obstacles, and avert disasters of various sorts, all without missing a TGIF party. Social bonds at Hybritech were created and strengthened over time as people worked together, played together, and, perhaps most important, persevered together through various crises and trials by fire. Sometimes it was (and still is) impossible for individuals and groups on the scene to discriminate between the fun and the toil, and even the stress. For many, the enjoyment, excitement, and satisfaction that they experienced were bound up with the challenges and risks that the enterprise accepted. Hybritech was extraordinary in its intensity. Howard Birndorf, Ted Greene, and Gary David were dedicated – each in his own way, and each for his own reasons – to the success of the enterprise, and, in concert, they imbued the company with a unique sort of drive. Hybritech embodied a 'work hard, play hard' ethic, and that was attractive to young scientists, and others, too. Under these conditions, the firm was able to elicit strong commitments and fervent loyalty from many of its employees. Desmond says: "The whole situation was pretty much ideal, I mean, really good employees, really motivated, an exciting business, expanding, so there were essentially no personnel or management problems." Dunham concurs: "It was good. We were all friends. There weren't any problems within the company at

[17] Ilene Schneider, "Hybritech Balances Creativity with a Marketing Orientation," Genetic Engineering News, November-December, 1985; pp. 12-13.

all. We had a lot of good times, a lot of going out and socializing, and going to Ted's house for parties, that type of thing."

The group of employees who were at the firm together from the beginning developed a distinctive local culture and a shared history. Within this social circle and its constellations of meaning, Hybritech was recognized as a special place. Greene was part of it, and he understood the 'magic.' He felt it, too, and recognized its organizational significance. He also sensed that it might be possible to foster it. He consciously tried to maintain the natural buoyancy of the organization, to promote high spirits, and encourage attachments to the enterprise. At the same time, however, Greene knew that Hybritech would eventually have to become a different kind of organization. He seriously intended to build the start-up into a major pharmaceutical company – Tom Perkins had convinced him that it could be done. He understood that the firm's entrepreneurial élan couldn't be sustained indefinitely, and that the day would come for it finally to be sacrificed. It was inevitable – the functional requirements of large organizational machineries would eventually rise to assert themselves and take precedence, and Greene knew it. In the midst of Hybritech's expansion, in 1984, he disclosed his vision of the future:

> IBM is a big company, and I think IBM is the finest human organization in the world. I mean, I won't try to compare them to the Catholic Church, but I think that outfit is a tremendous goal to shoot for. They have their problems, but when you look at what they have accomplished, and what they do for people, I think that is wonderful.[18]

When start-ups grow past a certain size, they invariably begin to adopt the airs of impersonal corporate machines. As Owen notes, "you start having to have an

infrastructure...you start getting a hierarchy, and you just can't put it off." It becomes more difficult and eventually impossible to maintain a sense of familiarity and intimacy within the organization. The distance grows wide between senior executives upstairs and people moving boxes around in the back, and, eventually, becomes a gulf across which the two groups travel only in extraordinary circumstances. Orders from the higher circles of management come down to employees like pronouncements from the gods. Messengers typically deliver them; personal visitations become miraculous. And workers who receive communiques are rarely, if ever, asked to respond. They aren't ordinarily called to the executive suites, unless perhaps to confess or to be appointed special envoys to the faithful. Common laborers usually aren't welcome at oak tables without formal invitations. Hybritech grew so quickly that separations of this kind appeared within a very short span of time. In 1980, Ted Greene was in Hybritech's laboratories every day. He knew everybody in the company by name. By 1983, Joanne Martinis would comment on how seldom he was seen in her department. Greene had forsaken the cell biologists: "He never comes into my lab anymore. The technicians in my lab don't even know who Ted is. They know he's the president of the company, but they've never talked to him."[19]

At Hybritech, social gaps were associated with real physical and geographic distances, too. For instance, as Greg Payne recalls, when Hybritech's manufacturing group moved into the building on Carroll Canyon Road in Mira Mesa, "it started to be a little more disjointed then, because now you had people over there, you know,

---

[18] Quoted in Grant Fjermedal, Magic Bullets, p. 135.

[19] Quoted in Grant Fjermedal, Magic Bullets, p. 134.

twenty minutes apart." People didn't see each other regularly, they didn't establish or maintain close relations, and, although they were employed by the same company, and perhaps traveled to one place or the other for occasional business or for TGIFs, they didn't necessarily get to know each other well. The two groups established separate identities. Moving to the new, spacious headquarters on Torreyana had a similar effect on the firm. Wang says: "By then, we were on the road to losing that real sense of camaraderie that we had originally. When we were at La Jolla Cancer, you know, we had these trailers...." There was something special about the trailers. Once they had passed into memory, stories about them were told and retold. The tales commemorated the ancestors and what the company had lost. Eventually, Hybritech came to be populated by two kinds of employees – those who had joined the firm when it was still in the trailers and those who had joined later.

As Walt Desmond points out, it's very difficult to resist the organizational changes that accompany commercial and industrial expansion: "I mean, you're successful and then you have to expand. If you talk to people, even in like restaurants, or something, thay say 'I want to only keep this restaurant. I do not want to expand,' but the pressure is on to expand. So, you have to just make this conscious, sort of rebellious effort to just say no." But, of course, you can't say no. In order to stay in business in a capitalist economy, you have to generate profits, and profits are measures of growth. To make it in business is to grow. The only choice is what business to be in. If you're successful and you want to stay small, the thing to do is to get out of the market that you're in, and get into another that has stiffer competition. Hybritech didn't get out of diagnostics and pharmaceuticals. It elected to stay and expand, and it

became very successful at staying and expanding. And the company changed. The sense that Hybritech was a special place, an unusual kind of place to work, didn't disappear overnight. Elements of the early corporate culture were maintained in various parts of the company, and especially the laboratories, independently, for a number of years. But, as company grew ever larger, it came increasingly to resemble, in both form and substance, a typical corporate bureaucracy. Eventually, after Hybritech was taken over by Eli Lilly, the firm became haunted rather than defined by its charm, charisma, or entrepreneurial spark. The spirit of the trailers lingered, to the extent that a few old-timers still remembered it, but only as a ghost in the machine.

BIG FISH IN A LITTLE POND

As Hybritech grew, it became increasingly differentiated. Development split off from cell biology and immunochemistry to become a distinct entity, and manufacturing followed its own evolutionary path, by and large, as it scaled up. Sales and marketing remained apart, preoccupied with its own ends and means, and detached from the groups that went to work in the firm's laboratories, while numerous other departments, organs, and offices began to appear to handle a wide array of technical and business tasks. All of these new units were given names, spaces, responsibilities, and spheres of authority. More and more people entered the firm in order to become attached to its new appendages. As a modern, profit-seeking corporate entity, Hybritech naturally adopted a conventional bureaucratic structure to systematize its operations, coordinate its workers, and regulate its operational metabolism. Once in place, the administrative apparatus did exactly what it was designed to do – it proliferated. Hybritech became increasingly complex and

immersed in the oversight and integration of disparate organizational functions, and the documentation, monitoring, and assessment of internal procedures and processes. It started to generate bigger piles of paper along with hybrid cells, antibodies, and diagnostic kits.

Each of the separate units in the company then began to stretch vertically. The company proceeded to erect formal hierarchies. From 1980 through the beginning of 1984, Hybritech assembled, in steady succession, a roster of vice-presidents to supervise operations in various parts of the firm. A big company needs big shots. They often serve functional purposes, but they are also indispensable accoutrements or accessories for the well-adorned large corporation. Hybritech's new executives were recruited from established diagnostic and pharmaceutical companies, to lend their expertise in applying industrial methods and solving industrial problems, and to add some polish and glamour to the firm's promotional literature. Tom Adams was the first. He arrived in April 1980 to direct R&D. The next month, Paul Rosinack followed and became the firm's vice-president of sales and marketing. Rosinack came to Hybritech from the Ortho Diagnostics division of Johnson & Johnson, where he had worked as a sales manager. Greene admired Johnson & Johnson, and wanted to emulate its commercial philosophy at Hybritech:

> They were a class act. J&J just did it right. They were ethical, they were professional, they did marketing strategies that created huge value, they locked into market franchises. J&J is one of the finest companies in the world. They screw up like everybody does, but if you go back over the last half-century or so, you have to conclude that they have been one of the most successful companies in the medical device business. OK, Merck, or Lilly, or whatever in pharmaceuticals, but J&J in devices, and that's what we were in.

Greene intended to borrow Johnson & Johnson's best practices by borrowing Johnson & Johnson's people. Rosinack was just the first of several senior Hybritech executives to come from J&J. In September of 1980, Cole Owen also arrived from Ortho to serve directly under Rosinack as director of marketing, while his boss then concentrated on assembling a sales force for the company. In October, Jim Jungwirth became Hybritech's first chief financial officer. He had previously been a vice-president and controller at a subsidiary of American Hospital Supply Corporation. Ron Taylor signed on as vice-president of manufacturing and operations in March 1981. When Taylor showed up from Allergan, Howard Birndorf surrendered the title of chief operating officer, and officially became the company's vice-president of corporate development. He had been devoting increasing amounts of time to external business deals rather then internal management duties, to in-licensing antigens and cell lines, out-licensing monoclonal antibodies, and exploring possibilities for corporate research and development partnerships, so the move seemed a natural one. Later in 1981, Guy Van de Winkel was named VP of international operations, and Michel Decoux was designated VP of European sales and marketing. Both were from Baxter and Hyland, and knew Ted Greene. Van de Winkel and Decoux established a subsidiary headquartered in Liege, Belgium. The firm 'adjusted' Hybritech kits for sale in international markets, and distributed and provided technical support for the products in Europe and around the world.

In 1982, Hybritech had products on the market, and was seeing its first significant revenue streams from sales of TANDEM diagnostic assay kits. Its business was still growing with no upper limits yet in sight, and the company again expanded

its executive ranks. It also reshuffled its deck of leadership cards, when strengths and weaknesses in the management team began to become apparent. Late in 1981, Gary David had organized a group to begin exploring applications of monoclonal antibodies in cancer imaging and therapy. Of course, using monoclonals for imaging and therapeutic purposes was a central component of Ted Greene's long-term development plan for the company. Greene wanted to turn Hybritech into a manufacturer of biopharmaceuticals. The research proceeded for a time as a skunkworks project. The company then decided that it was time to separate the effort formally from in vitro diagnostics, and to set it up as an independent branch of the R&D unit. So, in March 1982, Dennis Carlo was hired as vice-president of in vivo research and development and therapeutic manufacturing. He was recruited from Merck & Co. where he had held various positions, including director of developmental and basic cellular immunology, and director of bacterical vaccines and immunology, though he was still just thirty-eight years of age. He was hired for his expertise in developing biological therapeutics regulated by the FDA. Stealing a rising star from Merck's sky was a major coup for Greene and Hybritech. The formation of Carlo's division indicated that the firm was ready to make a serious push in therapeutics R&D.

The company made another important hire that same month. David Hale was named senior vice-president of marketing and business development. Hale came from BBL Microbiology Systems, a large subsidiary of Becton Dickinson in the diagnostics business. Prior to joining to BBL, Hale was a director of product management at Johnson & Johnson's Ortho division. For Ted Greene, "The fact that David was ex-J&J was extremely attractive." So, Hale remembers:

> I was sitting in Cockeysville, Maryland one day, watching it snow, and I got a call about a small biotech company in San Diego called Hybritech. Well, I had been involved at Becton Dickinson in looking at the use of monoclonal antibodies in diagnostics products, and in therapeutic products, and Becton Dickinson came to the conclusion that they were never going to work.

Hale didn't agree with that assessment. He believed that the technology had enormous potential. Still, the decision to make the move to San Diego was a difficult one, for several reasons. First, Hale was a vice-president and general manager at BBL, second in command at a company that, at the time, had a business generating total revenues of around $60 million annually. He was worried that, in terms of career advancement, accepting a position at a tiny start-up would mean taking a giant step backwards. Second, BBL mounted an effort to persuade him to stay, and promised, among other things, a substantial increase in salary (and far more than Hybritech was offering). Finally, his wife, Linda, was from New Jersey, and she wasn't thrilled about picking up to move to the West Coast. After wrestling with these dilemmas for a time, Hale decided to take the leap. He came into Hybritech above Paul Rosinack, who was already occupying the position of vice-president of sales and marketing. Greene explains: "Paul Rosinack was a good sales guy, but as we began to get to the point where we were going to pioneer a new immunoassay system, we decided that we needed somebody with real marketing prowess." Ron Taylor, who later ended up struggling with Hale for control of various aspects of the company's operations, offers a supplementary opinion about the episode:

> Ted Greene had a problem. Ted couldn't fire anybody. Hale was brought in to get rid of Paul Rosinack, who was VP of marketing, because Ted couldn't do it. So, he brought Hale in as senior VP of marketing. Why did we need a senior VP of marketing? Well, we

> didn't. So, that's what it was for, and a few months later, Hale fires Paul Rosinack.

The next new vice-president came to the company through a Baxter connection. David Kabakoff was added to the roster in February of 1983 as a replacement for Tom Adams. Hybritech's board wanted Adams to become the firm's chief technical officer, and to oversee all of the company's research and development projects. Kabakoff was to take over in vitro diagnostics R&D. He held a Ph.D. in chemistry from Yale. After completing his thesis research, he crossed the country to do postdoctoral work at UCSD. There, he worked in the laboratories of Murray Goodman and Nathan Kaplan. Both chemists maintained extensive industry connections. When Kabakoff was ready to leave UCSD in 1975, he tapped into these networks. He concentrated on looking for work in the commercial sector rather than academia. He would up at Hyland in Orange County, in a department that reported to Tom Adams. He also met Ted Greene while he was there. Later, as Hyland was disintegrating, and Adams left for Technicon, Kabakoff departed, too, around the same time, to become director of product development at Syva, Syntex's diagnostics subsidiary located in Palo Alto. Shortly after that, when Hybritech was in its infancy, Greene contacted him about returning to Southern California, but Kabakoff wasn't interested. Two years later, Greene asked again. Adams contacted him, too, and this time, the opportunity looked more attractive. Kabakoff explains:

> You won't find my name on any patents. I've never been particularly the inventive type, but somehow I've been able, I think, to kind of take stuff that people have invented, and listened to the commercial people, and the clinical people, and you know, really live in the middle, and turn things into commercial products. And, in the early stage of Hybritech, maybe it was just a little too theoretical and researchy. At

> some point around this time, it became clear that there were some major product development challenges, and they were in a position to recruit somebody to really lead that up.

Kabakoff signed on, and Adams took his step up. Another Baxter alumnus joined Hybritech's executive team at the end of March 1983. Tim Wollaeger came in to replace Jim Jungwirth as the firm's CFO. Wollaeger knew Ted Greene from Baxter.[20] After working with the company for several years as a "financial travel jockey," conducting analyses for corporate operations at various sites, Wollaeger was made general manager of Baxter's Mexico City operation, Travenol-Mexico. The plant manufactured most Baxter products, but not immunodiagnostics. When Hyland ran into trouble selling its goods in the U.S. and Europe, the company would look to Mexico as a dumping ground. Wollaeger remembers: "I'd get calls like, 'We've got sixty days dating left on this product, can you move it? Get the best price you can.'" While Wollaeger was in Mexico, Greene was director of Hyland's international sales, and the pair did some business together. Later, in 1981, after leaving Baxter, Wollaeger happened to find himself in La Jolla, working at National Health Laboratories, a chain of diagnostics labs under Revlon's umbrella. Wollaeger learned of Hybritech, and found out that Ted Greene was there. He also learned that he wasn't happy at NHL. He didn't feel that he fit in very well. "Baxter," he says, "had been sort a gentlemanly, well-educated kind of group of people. This was just rough and

[20] Bill Crean notes that at the heart of Hybritech's heterogeneous management team was a concentration of Baxter folk: "We had some people from Merck, some people from J&J, a lot of people from Baxter. There actually was sort of a Baxter clique. Among the top executives, Greene, Adams, Kabakoff, and Wollaeger had come from the company, and there more Baxter alumni in lower tiers of the hierarchy, too, including Russ Saunders, Bob Paradowski, Barbara McCampbell, Kim Blickenstaff, and Cream himself.

tumble, New York, yelling and screaming, and stuff like that." He left to become COO of a real estate development company in Santa Monica, but the business was in serious trouble. Wollaeger fought with the owners about financial strategy. Eventually, he gave up on the firm. He then decided to call on his old acquaintance from Baxter:

> I'd had two jobs in three years out here, and they'd both been kind of unpleasant, personally. I wanted to go to work for some respectable big company that knew what they were doing, someplace where I could fit in and do some stuff. My wife said, 'Before we go, before you embark on that, I'd like you to see what's here in San Diego.' You know, the kids were doing well in high school and all that kind of stuff. So, I went and talked to Ted.

Greene invited Wollaeger to come to Hybritech the following week to meet Brook Byers. A board meeting had been scheduled, and Greene thought that perhaps Byers could find a place for Wollaeger in one of the many biomedical companies in the Kleiner Perkins portfolio. By the time Wollaeger showed up, though, Greene had decided that he should come to work at Hybritech as the CFO. He was interviewed by Byers and other board members and handed the job the same day, April 1st, 1983. Ron Taylor says, again, "Wollaeger was brought in to fire Jim Jungwirth, who was chief financial officer. Ted couldn't do it. That was just part of his nature." Hybritech wanted a strategic planner and Jungwirth wasn't the right person for the job. Wollaeger says, "I think Jim was a financial accounting kind of guy, and the company needed more management." Taylor maintains that, in such circumstances, Greene's habitual approach was to rearrange the organization until the responsibility for firing fell to someone else. Wollaeger, however, says that Jungwirth "found another job and left. I'm not even sure if he was told I was coming in, and he was supposed to find

another job, or if he was going to run accounting and I was going to be part of the upper management team."

In October 1983, another shift took place in the upper levels of the firm. Brook Byers stepped down as Hybritech's chairman of the board, and the directors appointed Ted Greene to replace him. Greene was also designated chief executive officer. David Hale was named president and chief operating officer, and given a seat on the board. The directors had concluded that Hale would be better suited for the day-to-day operational duties of the president and COO, and that Greene's talents and energies would be best directed toward strategic planning, fund raising, public relations and investor relations, and working the Wall Street beat. Cam Garner was brought in to take Hale's place as senior vice-president of sales and marketing. He was an MBA who began his career in pharmaceutical sales at Upjohn and moved into management at a biomedical subsidiary of Corning Glass Works. Shortly after Garner's arrival, Larry Respess, Hybritech's patent attorney, gave up his position at Lyon & Lyon to join Hybritech as the company's general counsel.

To round out Hybritech's executive branch, Karen Klause came from Technicare Corporation, a subsidiary of Johnson & Johnson, in January 1984, to become Hybritech's vice-president of sales and marketing for in vivo imaging and therapeutic products. The company had anti-melanoma radioisotope-antibody conjugates in Phase III clinical trials, and was optimistically preparing for a product launch.[21] Klause had an engineering background. Technicare manufactured and sold

[21] Warren Froelich, "New Technique Discovered for Melanoma Diagnosis," San Diego Union, June 7, 1984, p. B-3.

imaging and nuclear medicine products – ultrasound, CT scanning, and MRI equipment, along with digitial radiography instrumentation. Hybritech's imaging tools were radiolabeled antibodies, so Klause was familiar with that market, and Greene, of course, was pleased to have another J&J person on board. The roster was complete. At the beginning of 1984, the upper management team steering Hybritech toward its momentous rendezvous with Eli Lilly consisted of Birndorf, Greene, Adams, Owen, Taylor, Carlo, Hale, Kabakoff, Wollaeger, Garner, Respess, and Krause. In the years following the sale of the company, these persons became involved as founders, officers, and directors in dozens of new entrepreneurial biomedical ventures in the San Diego. For the moment, though, they all concentrated on making Hybritech bigger.

Hybritech had followed a typical organizational blueprint in conceptualizing and naming its formal administrative practices. For a commercial enterprise that wants to scale up, the bureaucratic model is really the only one available. But bureaucratic structures of the kind represented on formal organizational charts are conceptual inventions. They're abstractions. Hybritech's actual organizational architecture (if the analogy holds up well enough to refer to one), took shape in the course of concrete social interactions. It was comprised of patterned associations that became conventional and habitual over time, and to which individuals in the company oriented their actions. In some cases, these associations were cooperative and productive. In other cases, they were sites of competition or conflict. Often, they were both, and they typically evolved over time as circumstances shifted around them. The firm grew as persons, materials, information, capital, knowledge, experience, and

so on, were accessed through such associations, through links tying individuals and groups together in interorganizational networks of resource distribution and exchange. Hybritech was comprised by a series of social networks that connected persons and teams within the company, but also extended beyond the boundaries of the firm to persons elsewhere, situated variously in different locales and social settings.

SOMETHING TO FIGHT ABOUT

As the company matured, the vice-presidents made many decisions that shaped it in consequential ways. They were handed executive powers and they exercised them to determine, usually in concert and negotiation with others, of course, how things would be done at Hybritech. To do so, they naturally drew on lessons from their varied backgrounds. The diversity of the group was engineered – not exactly by design, perhaps, but not wholly without intent, either. According to Cole Owen, the composition of the upper management team evinced a recruiting ethic:

> We had a group of people each of whom had been selected, recruited, brought in, because, to the best of our judgment, they were the best resources that we could get out of that company, or out of that area. And we were pretty conscious, pretty aware of trying to get people from different companies, so that we were getting the advantages of how something was done here, or how it was done there.

Bob Wang indicates that, at Hybritech, people and practices originating from different sources usually mixed reasonably well. Commitments to the company, tasks at hand, and common ends – along with time constraints and personnel shortages that made debate or indecision especially costly – apparently overcame any inherited biases:

> The actual systems that were implemented and used were hybrids of the various experiences of the people who had been in industry. There

> weren't people insisting that things had to be a done a certain way because this is how we did it at Calbiochem, or this is how we did it at Technicon. I mean, as long as it met the need, it was done, I think, if it seemed efficient.

The deliberate cultivation of diversity as a means of enhancing organizational capabilities is a notion foreign to many institutions or groups dedicated ostensibly to innovation or the accumulation of knowledge – academic departments, disciplines, and schools of thought are perhaps the most striking examples. But Tim Wollaeger's comments suggest that, in the world of business, there was nothing unusual about Hybritech's style of organizational learning. He says that one of the most valuable things that he learned during his tutelage under Baxter CEO, Bill Graham, was how to source information from other companies, through personal connections:

> I worked for Graham, right under him for three years, and he'd sort of say, 'Figure out this problem on currency, but before we get into it, let's call General Motors and IBM, and ask them what they're doing.' And we'd call, and more often than not, they'd say, 'God, we never even thought of that problem. What are you doing?' We'd tell them and they'd say, 'That's a great solution.' So, he was ahead of things, and there was none of this, 'Oh, that's a big problem for us to tackle, let's wait.' Graham was just boom, boom, boom. I think there was a lot of that attitude at Hybritech. You always rely on, 'Well, how did R&D get anything done at Baxter?' or 'How was the sales force set up?' or 'What kind of people did you hire?' And Kleiner Perkins had a lot of other companies, and sometimes we'd call up those that were ahead of us to see what they were doing, like Genentech or Home Health Care of America. Home Health Care was also Kleiner Perkins, and also a bunch of former Baxter guys, up in Orange County.

Each of Hybritech's vice-presidents contributed knowledge of useful and successful practices to the start-up, and, by and large, the organization was able to take advantage of what they knew or could find out. But the process also brought some discord and fragmentation to Hybritech, along with cultural depth. When Hybritech

began organizing departments, erecting hierarchies, and establishing vice-presidencies, it effectively created new bureaucratic turf. Once occupied, the sod became contested and defended, to no one's great surprise. Bill Crean says of the company's top managers: "These were very strong people, and teamwork, the team orientation, was just starting to evolve. All these different personalities wanted to emerge as the leader, so it was kind of a difficult deal." Bob Wang observed that, "There was a lot of infighting among the vice-presidents, concerning who got credit for what." Cole Owen reports that, within this group of people who were used to competing with others for resources, and had proven that they were good at it, "There was a lot of pushing and shoving." Still, the start-up environment didn't encourage pettiness. If there were fights, they were usually about issues of some substance. Owen adds that, usually, in a start-up environment:

> Nobody gives a rat's ass if you pick up a ball and do something that might otherwise have been deemed to be in their court, because they don't have time to do it anyway. So, if you want to do it, have at it. Whereas, if you're in AT&T or GM, when you pick up a ball in somebody else's court, they might get pretty territorial about it.

At the top of the emerging pyramid, Ted Greene and Tom Adams waged some titanic battles. They fought, for instance, about whether Hybritech should manufacture an automated analyzer to read the company's clinical assays. There were two philosophies on the matter within the firm. Greg Payne articulates the pro-analyzer position: "We were never really an instrument company, which is one of the things that hurt us, because that's what out customers really wanted. We made great assays, but they also wanted automation, and we couldn't provide any." Proponents argued that competing in the manufacture of instruments would be crucial for long-

term survival in clinical testing markets. The contrary philosophy was founded on the premise that companies in the field wouldn't be able to develop leading technological capabilities in both reagent chemistry and hardware. They would have to choose which to excel in, and, clearly, Hybritech was already an antibody company. But Adams had previously been involved in very successful instrumentation projects at DuPont and Technicon. He and Greene found themselves at odds on the issue.

Greene remembers: "This is where I let Adams have his way. He wanted to do what I always called 'Big Iron.' He wanted to develop a fully automated, random access immunoassay analyzer. And I remember thinking, 'You know, that's what Abbott does.'" Generally, if Abbott did something, Ted Greene didn't want to touch it, but he gave in. Hybritech's first analyzer was a manual spectrophotometer called the PHOTON.

It was released in 1983. The company also manufactured a batch analyzer, called the PROTON, and, later, an ICON reader, as well. After the PHOTON introduction, the company commenced with development work on the next generation instrument – Adams' pet project, the PHOTON Elite, as it was called. Adams wanted to design a complete testing system, a sophisticated, fully automated, programmable analyzer in a box. The goal, in essence, was to reduce the lab technician's role to adding a specimen and waiting for the analyzer to deliver all of the answers. Hybritech worked on the hardware in a partnering agreement with Toyo Soda, a Japanese firm. The project was eventually abandoned. It was, Greene relates, a major technical undertaking, and "it got us really deeply in with the Japanese, which was a horrible

idea, because of the language and the culture, and ugh! And it finally just died. But that's what Tom wanted to do."

Adams also got into a scrape with David Hale, not long after Hale arrived to take over sales and marketing in 1982. "Within six months," Greene remembers, "I had Tom Adams in my office screaming that we had to fire this guy, Hale, he's going to ruin the company, and I'm going, 'Tom! Tom! Don't do this to me!'" Greene explains the problem:

> Dave was classic marketing and Tom was classic research. Tom's whole view of customers was that customers will act rationally. They will want the best-performing products, and the best cost-effectiveness, and so on and so forth. Dave, on the other hand, had come up through the sales force, and he had harangued customers for years...you know, guys like Adams believe that marketing is a necessary evil and Tom just couldn't stand that Dave was doing some things that he wanted to do.

The differences between Hale and Adams came to a head when Hybritech decided to market its pregnancy tests to physicians' offices, as well as clinical reference laboratories. The economics of selling to the two kinds of customer are very different. Clinical labs are big customers. They buy kits at high volumes. Physicians are small customers. They buy just handfuls at a time. Hybritech had its own sales force, but it wasn't going to pay to have salespersons dropping in at doctors' offices. The numbers didn't make any sense and the sales team would revolt, so the company had to come up with another way to get into the market. Adams struck out independently and negotiated a marketing deal with American Home Products, a company that, according to Greene, "was selling drugs to these doctors that were consistent with pregnancy testing." In Adams' scheme, Hybritech's pregnancy tests

would piggyback into the new marketplace. Hale was simultaneously developing a relationship with an entrepreneurial group in Connecticut that was starting a business based on a new approach to marketing devices to physicians. Greene was presented with two competing proposals. "Since this was a marketing decision," he says, "I ended up saying, you know, 'Dave's in charge of marketing. We've got to go with his approach.' So, that's what we did. It didn't work. Tom never forgave me for it. That was kind of the beginning of the end."[22]

By this time, Dennis Carlo had come to Hybritech to run the in vivo imaging and therapeutics research program, and David Kabakoff had arrived to take over in vitro diagnostics R&D. The research operation and its various component projects were becoming increasingly complex and disconnected, both organizationally and technically. The company's imaging and therapeutics works were gobbling money voraciously, and tending to veer off product development paths according to the dictates of their own internal logics. The technical problems were so specialized and esoteric that it was difficult to keep independent research groups focused adequately on the entire range of critical product development requirements. The board and the upper management team believed that if Adams rather than Greene – who, as CEO, was looking after the entire company, and was busy with responsibilities in many other areas – became the central figure at the top of the R&D reporting structure, then the coordination of research efforts could be improved. The idea was that Adams would take a step back from day-to-day operational control of the R&D units, and

[22] Adams evidently forgave Hale because when he left Hybritech a few months later to found his own company, he asked Hale to lend his expertise. Greene says, "It was very satisfying to me that one of the first guys that Tom recruited to his board of directors was David Hale."

work to maintain the technical integration of the various experimental programs. It was apparent, Greene says, that "Tom didn't really want to do it."

> My board was becoming frantic because they viewed Tom as a great visionary and a brilliant guy, and so on, but with this huge R&D budget, huge burn rate, and all these complex programs underway, they thought, and I had to agree with them, that Tom just wasn't an administrator. What they wanted him to do was to come up here and be the visionary, and to have guys under him who would really run the programs. Tom found himself increasingly kind of sitting in his office kind of staring at the wall.

Adams' was numbering his days at Hybritech. He would leave in June of 1984, along with Howard Birndorf, to start a new company, called Gen-Probe, the first of many San Diego biotech firms with ties to Hybritech. There were other run-ins among the vice-presidents. Usually the scuffles were minor, but they sometimes resulted in significant organizational restructurings. One such incident involved David Hale and Ron Taylor. Their relations were professional and cordial, but cool: "David Hale didn't like me," Taylor says, "I don't know if that's too strong, but it's probably correct." When Hale's sphere of authority within the firm was expanded from sales and marketing to include operations, and he was named COO, he and Taylor began working closely together, out of necessity. But Hale was, in a sense, then trespassing on Ron Taylor's ground. Or, that's how Taylor saw it, anyway. Taylor believed that he should have been appointed COO:

> Hale ultimately became executive vice-president and chief operating officer, a position that I thought I should have had. That's fine. He got the job. He had a guy who had worked for him in two prior companies, who was an operations guy that he wanted to bring in, into my job. First he tried to bring him in working for me, and the guy wouldn't come under those circumstances, so I could see the handwriting on the wall, that Hale was basically trying to bring this guy in because he was his buddy.

The buddy was Chet Damecki, who had worked with Hale at BBL Microbiology Systems, and, prior to that, at Ortho. Taylor decided that he didn't want to continue in his position given these particular circumstances, so he tried to identify something else that he might do in the company. He intended to step aside so Hale could let Damecki in. Taylor went to see Hale, and said, "'Look, I've been the biggest critic of our international operations, or lack thereof. Why don't you put me into a job where I can line up some international distributors and get some stuff going, and that will open up the operations job. You can bring Damecki in to that position.'" Hale was pleased to find a volunteer for the international operation. The perception in San Diego was that more needed to be done and could be done in overseas markets. The Belgian international headquarters, however, was operating without close supervision, and it was difficult to implement changes from California. Taylor had never worked in sales before, but after wrestling for years with the tolerances on Hybritech's products and manufacturing systems, he imagined that he could tackle just about any kind of problem. He boosted Hybritech's international revenues during his two-year stint in the position. So, the conflict was resolved, but episodes like this one showed that the company had changed.

Beneath the VPs on Hybritech's organizational chart, activities and interactions became more structured. Some employees were happy to settle into fixed positions and to follow regular procedures; climbers seeking routes to higher elevations found that trails had already been broken and roped. Ascents became routine. For individuals, the firm's expansion, maturation, and gradation meant that

statuses, roles, duties, relations of authority, chains of command, avenues of advancement, and levels of compensation all became more precisely defined. Life at Hybritech became more predictable. The organization was working to make itself, by degrees, more rigid and inflexible, with some success. Departmental boundaries became less fluid and permeable, and social divisions naturally accompanied functional divisions. Animosities and rivalries, between marketing and manufacturing, manufacturing and development, and development and marketing, for instance, became ordinary facts of organizational life. The usual divides between us and them, the good guys and the bad guys, and labor and management all appeared. Bob Wang also mentions the gap between the vice-presidents and the managers just below them (the group to which he belonged): "I think that the people who really made the company were at the project director level or below, working as a team. People put their egos aside for a period of time, and didn't interfere with accomplishing what needed to be accomplished."

On a split that emerged within R&D between diagnostics and therapeutics, Russ Saunders says: "The division was there, I mean, you could feel it. They were more into research, and they were more oriented toward therapeutics as far as their goals were concerned. You could feel the division." The relationship between the diagnostics and therapeutics programs was important at Hybritech. Initially, diagnostics was the cock of the walk. The success of the TANDEM kits had put the place on the map. Later, though, because Hybritech advertised itself as pharmaceutical company, and raised huge sums of money to fund research on imaging and therapeutics, the relative status of the diagnostics program started to decline.

Therapeutics was glamorous. The diagnostics business was doing very well, but the division couldn't throw its weight around. It didn't have the run of the place, and, perhaps, the diagnostics people didn't feel adequately appreciated. When imaging and therapeutics work got underway at Hybritech, it was no longer 'all for one, one for all.' The company had gotten big. It had been successful, and it now had big shots directing big divisions that did big things with big money. This was serious business. In the early days, working at Hybritech was fun. Later, people still had fun, sometimes. And then, they went back to work.

BIG SCIENCE

Late in 1981, the company had decided that it was ready to tackle some attention-getting problems in science and medicine. The firm's new IgE kit was doing well, and, as Hybritech expanded its presence in diagnostics markets, Abbott and a few other competitors, at least, noticed.[23] But clinical testing products don't capture imaginations, excite people on the street, or create the kind of stir that prompts stock markets to surrender millions of dollars to an entrepreneurial start-up at the first opportunity. After Russ Saunders and Bob Wang took over responsibility for in vitro product development, and turned the TANDEM assay into a fairly robust system, Gary David started pushing some of the company's research in new directions. He began investigating in vivo imaging and therapeutics applications of monoclonal

[23] Eventually, Abbott and Hybritech met in direct competition. The battle quickly spilled out of the marketplace into the courts. Suits and countersuits were filed alleging intellectual property and antitrust violations. Greene's worst fears had been realized. Hybritech had irritated the gorilla. The company's legal arguments were sound, however – Hybritech prevailed – and it wasn't long before Eli Lilly was picking up the tab for the company's legal expenses. Abbott picked the fight, but the next day had to contend with Hybritech's big brother. See Warren Froelich, "Mighty Abbott, Tiny Hybritech Locked in Legal Battle," San Diego Union, December 18, 1985; p. B-1.

antibodies. Hybritech intended to inject radiolabeled monoclonals into cancer patients, to light up tumor cells for diagnostic purposes, or to hunt them down and destroy them with beta-emitting radioisotopes.[24] One of Ivor Royston's principal motives in starting the company three years earlier had been the chance to make monoclonal antibodies that could be employed to treat cancer. Using revenues from diagnostics sales to leverage a therapeutics program had been part of the Hybritech plan since the summer of 1978, when Kleiner Perkins had first become involved with Royston and Birndorf, the two original entrepreneurs. In fact, the idea had crystallized the seeding deal. In the course of his due diligence on the investment opportunity, Brook Byers talked to pharmaceutical executives about the long-term possibilities for monoclonal antibodies in medicine. They confirmed what Royston had told him – these things could be directed against cancers. The venture proposed by the two entrepreneurs became attractive to the risk capitalists when markets for pharmaceuticals became conversation pieces.

At the board level, there was constant questioning about it – when would the firm be ready to start on cancer research? Everyone understood that pharmaceuticals were the big time. That's where the company's financial backers expected the big payoff from their investments in hybridoma technology. When Ted Greene came on board as Hybritech's president in the spring of 1979, he explained the theoretical utility of monoclonals as imaging tools and anti-cancer agents in his revised plan for the business. He also suggested that Hybritech could expect to see revenues from

---

[24] The story of early in vivo projects at Hybritech and collaborations with Dr. Sam Halpern at UCSD and Dr. Stanley Order at Johns Hopkins is told by Grant Fjermedal in Magic Bullets, New York: Macmillan, 1984.

therapeutic products as early as 1984.[25] While promoting Hybritech's IPO in October 1981, he announced boldly: "Our goal is to become a major pharmaceutical house – say, like Merck & Co., within 10 years."[26] In the red herring, the preliminary prospectus for the offering filed with the SEC, the company highlighted its plans to develop antibodies for in vivo use: "Upon completion of preclinical animal trials now underway, Hybritech intends to seek FDA approval for studies in humans of certain imaging and therapeutic products incorporating monoclonal antibodies."[27] The valuation of the company turned on its potential as a manufacturer of pharmaceuticals, so the directors and executives encouraged the scientists, and no expense was spared. For five years, from 1981 to 1986, when he left the company, Ted Greene probably spent more hours chasing money to fund Hybritech's monoclonal imaging and therapeutics research than on any other executive task.

Hybritech began its in vivo program by establishing a relationship with Sam Halpern, a specialist in nuclear medicine at the UCSD School of Medicine and the La Jolla VA Hospital. The plan was that the company would supply the antibodies, Halpern and the Hybritech researchers would work together on the labeling chemistries, and they would test imaging protocols on animals, first, in Halpern's VA laboratory, and later, on human patients in clinical trials at the hospital. Gary David and Richard Bartholomew, along with chemists Jim Frincke and Charlie Lollo,

---

[25] Howard E. Greene, "Hybritech, Incorporated," May 1, 1979.

[26] Craig D. Rose, "Magic Bullet That Missed: Hybritech Did a Lot Right, But Lilly Pulls Plug on New Drugs," San Diego Union-Tribune, October 26, 1993, p. C-1.

[27] Hybritech, Inc., "Initial Public Stock Offering Prospectus," October 28, 1981; p. 11.

comprised the core of Hybritech's scientific team. At UCSD, Halpern was assisted closely by radiopharmacist Phil Hagan. By all accounts, the group got on very well, and had a lot of fun as they worked. They became friends. Hagan still plays racquetball with Gary David. Halpern found the collaboration with the industrial scientists to be stimulating and rewarding. He describes his co-researchers as "brilliant" (even if, as chemists, they lacked knowledge of biology at systemic levels), and says, "There were times when the intellectual ferment was better than at any university that you've ever been at. Everybody stood up and spoke their minds, everybody. At these retreats, you sat there and people would blast away, but it was never personal. It was always the science, which I really loved, you know."

Halpern was not initially enthused about monoclonal antibodies. He had first heard about them when Ivor Royston moved into the 'hemoc' (hematology/oncology) department at the La Jolla VA Medical Center in 1977. Royston told him excitedly that, when injected into cancer patients, monoclonal antibodies targeted against specific cancers would accumulate in tumors and glow like beacons in the night. Halpern wasn't impressed. He knew a lot about tumor physiology and the pharmacokinetics of antibodies – he had been trying for some time to put high molecular weight proteins into tumors. He felt that tumor capillaries were too few and too small for monoclonal antibodies to map tumors in any comprehensive way, and worse, he knew that, in many tumors, there were massive shunts just about everywhere. Inside cancerous growths, antibodies encounter powerful convection

currents that try to flush them out.[28] Imaging with polyclonal antibodies is problematic because cross-reactive antibodies target tissues other than the specific tumor to be mapped. Monoclonal antibodies, Halpern thought, might do a better job of delivering radioisotopes to the right addresses. However, an even greater problem than specificity in cancer imaging with antibodies is getting immunoglobulins to stay put in tumors so that gamma emissions from the radiolabels they carry can be measured. Halpern says, "I kept telling Ivor, 'This will fail. This will fail. This will fail.' So, he prevailed on me to do a study with some iodinated antibody, and we did, and as I predicted, the amount in the tumor was low, very low. But, the amount in the tumor was higher than the stuff that I was fooling with. Under those circumstances, it became a better mousetrap for me."

At the time, ^{125}I was the radioisotope most commonly employed for imaging purposes, but Halpern didn't like it because it emitted beta particles as well as gamma radiation. Gamma radiation doesn't harm local tissues. It sprays particles for several feet. Patients have to be isolated, because others who come around them might be irradiated, but they don't get the dose themselves. Beta radiation is relatively weak in comparison. Beta particles travel only very short distances. In the body, they impact surrounding tissues, so they're desirable for therapy, but not for imaging. For imaging purposes, instead of radioiodine, Halpern wanted to try indium, a pure gamma emitter.[29] The labeling chemistry for indium, however, was far trickier. At the time,

---

[28] See Rakesh K. Jain, "Barriers to Drug Delivery in Solid Tumors," Scientific American, July 1994; pp. 58-65.

[29] Halpern explains the difference between beta and gamma emissions in radiation therapy contexts. With pure beta emitting isotopes, he says, "the only thing that comes off the patient is braking radiation,

there was no reliable method for tagging antibodies with indium. Radioiodination was straightforward, standardized, and routine, but Halpern knew that chelating indium to antibody proteins would take some work, and that he didn't possess the necessary expertise for it. He recognized that Hybritech's scientists did, so the collaborators began experimenting with indium, and a few other alternatives to iodine for imaging applications.[30]

---

which is known as bremsstrahlung. It's a German word that means braking, because the beta particle swings around the nucleus in a crack the whip thing. And, as it cracks the whip, it starts to exceed the speed of light. It can't exceed the speed of light because Brother Einstein said that it couldn't, and it can't, but if it gives off energy, it will slow down, and so it gives off the energy, the braking radiation. It slams on the brakes and off goes this photon. But that's low energy stuff, so you can treat the patient on an outpatient basis. And today, it's a big damned deal, because if you hospitalize somebody, especially if they're in an isolation room, you're looking at a couple thousand bucks a day. It pushes the cost way up. Iodine, you're going to have to keep them hospitalized because it has a huge gamma component. There are five or six photons that come boiling off of iodine, some of which are very high energy, they can go all the way to up to 700 keV or better, and there's a significant percentage. Even the principal photon, 82% comes off at 364 keV, and so you've got well over 90% coming off at 364 or greater, so you're going to shower everyone around you. And it's got an eight day half-life, so you're going to shower a long time. So, you're going to hospitalize them, or else you're going to have to use very small doses.

[30] P. Stern, S. Halpern, P. Hagan, G. David, and W. Desmond, "Comparison of an I^{125} labeled monoclonal anti-tumor antibody with Ga^{67} in a nude mose-human colon tumor model," Clinical Nuclear Medicine 5 (suppl.), 1980: S19; S.E. Halpern, P.H. Stern, P.L. Hagan, A.W.N. Chen, G.S. David, W.J. Desmond, T.H. Adams, R.M. Bartholomew, J.M. Frincke, and C.E. Brautigan, "Radiolabeling of monoclonal anti-tumor antibodies, comparison of I^{125} and In^{111} anti-CEA with Ga^{67} in a nude mouse-human colon tumor model," Clinical Nuclear Medicine 6, 1981: 453; P. Stern, P. Hagan, S. Halpern, A. Chen, G. David, T. Adams, W. Desmond, K. Brautigan, and I. Royston, "The effect of the radiolabel on the kinetics of the monoclonal anti-CEA in a nude mouse-human colon tumor model," pp. 245-253 in Hybridomas in Cancer Diagnosis and Treatment, New York: Raven Press, 1982; S.E. Halpern, P.L. Hagan, P.R. Garver, J.A. Kozol, A.W.N. Chen, J.M. Frincke, R.M. Bartholomew, G.S. David, and T.H. Adams, "Stability, characterization, and kinetics of I^{111} labeled monoclonal anti-tumor models," Cancer Research 43, 1983: 5347-5355; P.L. Hagan, S.E. Halpern, A.W.N. Chen, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "Comparison of In^{111} Fab and whole In^{111} in anti-CEA monoclonal antibody (MoAb) in normal mouse and human colon tumor models," Journal of Nuclear Medicine 24, 1983: 77; S.E. Halpern, R.O. Dillman, P.L. Hagan, J.D. Dillman, I. Royston, R.E. Sobol, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "The clinical evaluation of In^{111} labeled monoclonal anti-melanoma antibodies for human scanning," Journal of Nuclear Medicine 24, 1983: 15; S.E. Halpern, P.H. Stern, P.L. Hagan, A.W.N. Chen, R.M. Bartholomew, J.M. Frincke, G.S. David, and T.H. Adams, "The labeling of monoclonal antibodies with In^{111}. Technique and advantages compared to radioiodine labeling," in Radioimaging and Radioimmunotherapy, eds., S. Burchiel and B. Rhodes, New York: Elsevier North Holland Biomedical Press, 1983; R.O. Dillman, K.F. Witztum, J.B. Dillman, P.L. Hagan, M. Clutter, J.M. Frincke, R.M. Bartholomew, G.S. David, D.J. Carlo, and S.E. Halpern, "Immunoscintigraphy with $indium^{111}$ conjugated monoclonal antibodies," in Protides of the Biological Fluids, Vol.32, , ed. H. Peeters, Oxford: Pergamon Press, 1985; S.E. Halpern, R.O. Dillman, K.M.

Initially, Tom Adams had a place on the periphery of the in vivo group, from which he monitored the progress of the research. At the beginning of 1982, he arranged for the company to participate in clinical trials of monoclonal radioimmunotherapies in human beings with Dr. Stanley Order at Johns Hopkins University. Order was trying to treat hepatomas, liver cancers. He had been using polyclonal antibodies with iodine, and contacted Hybritech when he heard about monoclonals. Hybritech persuaded him to try yttrium rather than iodine to irradiate tumors because it was a purer emitter of localized beta radiation.[31] Unlike iodine, yttrium doesn't shower radioactive gamma particles everywhere around the room in which the patient sits in isolation, so treatments could be administered on an outpatient basis. "Yttrium has a half-life of around 70 hours, and because it's pure beta," Halpern says, "you can shoot 'em up and ship 'em out." The problem with yttrium, like indium, was that no one had yet figured out how to attach and stabilize it on an

---

Witztum, J.F. Shega, P.L. Hagan, W.M. Burrows, J.B. Dillman, M.L. Clutter, R.E. Sobol, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "Radioimmunodetection of melanoma utilizing In^{111} 96.5 monoclonal antibody – a preliminary report," Radiology 155, 1985: 493-499; P.L. Hagan, S.E. Halpern, A. Chen, L. Krishnan, J. Frincke, R.M. Bartholomew, G.S. David, and D. Carlo, "In vivo kinetics of radiolabeled monoclonal anti-CEA antibodies in animal models," Journal of Nuclear Medicine 26, 1985: 1418-1423; J.M. Frincke, C.H. Chang, C.N. Ahlem, G.S. David, R.M. Bartholomew, L.D. Anderson, P.L. Hagan, S.E. Halpern, and D.J. Carlo, "Pharmacokinetics of bifunctional antibody delivered In^{111} benzyl EDTA to colon tumors in nude mice," Journal of Nuclear Medicine 27, 1986: 1042; P.L. Hagan, S.E. Halpern, R.O. Dillman, D.L. Shawler, D.E. Johnson, A. Chen, L. Krishnan, J. Frincke, R.M. Bartholomew, G.S. David, and D. Carlo, "Tumor size: Effect of monoclonal antibody uptake in tumor models," Journal of Nuclear Medicine 27, 1986: 422-427; S.E. Halpern, P.L. Hagan, A. Chen, C.R. Birdwell, R.M. Bartholomew, K.G. Burnett, G.S. David, K. Poggenburg, B. Merchant, and D.J. Carlo, "Distribution of radiolabeled human and mouse monoclonal IgM antibodies in murine models," Journal of Nuclear Medicine 29, 1988: 1688-1696.

[31] S.E. Order, J.L. Klein, P.K. Leichner, J. Frincke, C. Lollo, and D.J. Carlo, "^{90}Yttrium antiferrin – a new therapeutic radiolabeled antibody," International Journal of Radiation Oncology, Biology, Physics 1986, 12: 277-281.

antibody protein.[32] Hybritech's Jim Frincke eventually worked out the conjugation chemistry, and, two years later, after the FDA approved the planned research, the trial was finally ready to proceed. The first monoclonals were injected into patients with liver cancer the following year, in 1985.

Sam Halpern is still sore that he wasn't given a chance to do the first clinical trial of a therapeutic monoclonal.[33] He maintains that using yttrium was his idea, and believes that Order was selected because he was a high profile cancer researcher, good with public relations, and with good with the press: "Stanley was a guy who, he could mesmerize you, he could. He should have been a United States senator or something like that, because when you sat and listened to Stanley, he blew you away. He just blew you away. And he was bright, but let's say that he was less direct with his data than I was." According to Halpern, Hybritech wanted Order to help market and advertise to broad audiences the idea of monoclonal antibodies as 'magic bullets' in the fight against cancer. As it turned out, the trials were well publicized, but the results were controversial. It was difficult to determine whether the appearance of monoclonal antibodies in liver tissues had anything to do with their special affinity for

[32] There was another serious problem, as well. Yttrium injected into the bloodstream isn't cleared from the body – it accumulates in bone marrow. Halpern compares the pharmacokinetics of iodine and yttrium: "The iodine circulates around, it goes into the tissues, once it gets into the tissues, it starts dehalogenating like mad. It comes out and it's kicked out in the urine. In the case of yttrium, the stuff stays in the body, and the stuff is swishing through the bone marrow, and the bone marrow becomes the critical organ. And your platelets sag to zip, and your granulocytes drop like a rock, your lymphocyte count goes way down, and you hope they go back up."

[33] Halpern's collaboration with Hybritech continued into 1986.

hepatomas. The body naturally clears labeled antibodies through the liver. As Gary David says, the researchers "may just have been putting an isotope onto a protein."[34]

As the in vivo work had gotten underway, preliminary findings in animals were suggestive, but they also showed Hybritech's scientists just what they were up against. Biology is unnerving in its complexity, and it was defeating the company's attempts to use antibodies for imaging and therapeutic purposes. The scientists weren't giving up, but they hadn't discovered much cause for optimism. In 1979, Ted Greene had predicted revenues from therapeutics in five years. When 1984 rolled around, however, none could be spotted anywhere on the horizon. The language of the company's annual report to shareholders, the last the company would produce before its sale to Eli Lilly, is telling. In a section introducing the firm's in vivo research, Greene and Hale announced the commencement of Phase III trials on the first tumor imaging product, an anti-melanoma antibody-indium compound. They declared that early results were "encouraging," and stated that, "We continue to

[34] In the Johns Hopkins collaboration, poor design was not restricted to the trial protocol. Bob Wang tells the story of an incident in which a Hybritech lab technician shipped some indium-labeled soluble antibody to Johns Hopkins inside a lead pig. Lead pigs are radiation-shielding containers that weigh about five pounds. Apparently the tech stuffed the inside of the pig with kit wipes – some kleenex, basically – and then put the container in a box with paper packed around it. The paper must have become compressed allowing the pig to tumble around inside the box. By the time the package reached Johns Hopkins, Wang says, "It was wet on the outside. The RSO [radiation safety officer] at JHU puts a monitor up to it, because this is what the regulations for handling radioactive material call for, and the thing just pegs the monitor, right? This thing is hot, whoa! So, of course, the RSO is required by DOT regulations to call FedEx, who shipped it. FedEx then calls Hybritech, and the DOT. The DOT gets on our butts. The DOT threatens to fine us. Well, what they did, the DOT had to go back and track which delivery truck took it to JHU, what airplane flew it from Memphis to Baltimore, what truck carried it to this FedEx place in Memphis, and all the way back to where it was shipped from, Hybritech. And I heard a rumor that they had to close down one of the conveyor belts at the FedEx facility in Memphis so that the DOT people could monitor to see if it was contaminated. And, fortunately, I didn't hear that there was any other contamination, other than maybe at the end. Maybe that was when the vial had broken and the box had gotten wet. So, think of how much money that cost. I don't think Hybritech ever had to pay any money to cover the costs, but that was a pretty severe incident."

believe 1986 is a reasonable target date for our first approval of a tumor imaging product." They also touted the FDA clearance of an IND (investigational new drug) application for the liver cancer trials to be conducted at Johns Hopkins. The FDA was going to let the company inject human beings with yttrium-labeled antibodies. In addition to this news, Greene and Hale wrote:

> As we anticipated, the development of antibody-based compounds that may treat and cure the most prevalent forms of cancer has been our most challenging technical undertaking in your Company's six year history. Our accomplishments of manufacturing our first experimental drug is truly evidence of the progress we have made toward our goal of becoming a major pharmaceutical company.[35]

That was it. Hybritech's scientists had managed to stick some yttrium on some antibody proteins. This was no mean feat. When the researchers first tried it, the yttrium labels had repeatedly fallen off the antibodies to go where they would in the tissues of animals used for experimentation. Now, Hybritech had shown that, after injecting the conjugates into animals, the radioisotope remained securely in place. Beyond that, however, the company did not have much progress to report. After several years of working intensively with anti-cancer antibodies, Hybritech hadn't conducted its first human trial. The previous year, the company had revised its schedule for introducing a cancer therapeutic – 1988 was the new estimate, "based on results to date."[36] The firm's annual reports carefully avoided mention of the obstacles that the company was attempting to surmount. The trouble with the yttrium was noted – "Hybritech scientists have overcome formidable technical difficulties in

---

[35] Hybritech, Inc., "1984 Annual Report," April 29, 1985.

[36] Hybritech, Inc., "1983 Annual Report," April 30, 1984.

achieving a stable linkage of antibody to yttrium"[37] – but only after the problem had already been solved. The company reported the fix, but it had never previously acknowledged the difficulty. There were plenty of technical challenges, of course, that the firm elected not to reveal or discuss with shareholders. And not all impediments were biological. Gary David speculates that, in addition to the obstinacy of nature, Hybritech's failures in therapeutics had to do with a lack of organizational focus:

> The NIH stuff was going. The Stan Order, Johns Hopkins stuff was going on, and meanwhile, we were trying to put out our own product, and somewhere in there, we also got involved with Ivor, in labeling his antibodies. This was when he started his next company, IDEC, and wanted to use anti-idiotype antibodies labeled with yttrium to target lymphomas. This diluted out our efforts quite a bit, with all these programs going on.

Maybe the science was too big. In any event, despite the absence of clinical successes, the company was learning a great deal about the possibilities and limitations of using monoclonal antibodies to detect and treat cancer, and much of the research was published.[38] As long as trade secrets were not divulged, and patents were filed in order to secure control of proprietary techniques, the company encouraged the scientists to release their findings and to maintain connections in scientific communities and academic disciplines. Gary David gives the rationale:

> Part of our philosophy was, it was a new technology, a new game, and we needed to get the word out, we needed to educate the community, and we needed to be a credible group. And the way you do that is to publish in quality journals. We gave a lot of papers at meetings and did

---

[37] Hybritech, Inc., "1984 Annual Report," April 29, 1985.

[38] Hybritech scientists presented eighteen papers and posters at the annual Society of Nuclear Medicine meetings held in Washington, D.C.. during June 1986.

> a lot of publishing, and in many cases, we had to be a little careful. I remember one instance in which we were all scrambling to get the patent application in because we had a presentation at a meeting coming up in a week.

A good deal of fundamental immunological knowledge and some innovative advances in antibody technology came out of efforts by Hybritech's cell biology and immunochemistry programs to design better antibodies for in vivo use. The biologists worked on methods for fusing human lymphocytes with myelomas, in order to make human monoclonal antibodies.[39] Gary David's chemists developed 'switch' antibodies, monoclonals with immunoreactive properties that can be turned on and off chemically. They also invented novel methods for chelating metals to antibody proteins.[40] In 1985, the company brought in a team of molecular biologists to develop new 'chimeric,' 'humanized,' and 'bifunctional antibodies' – recombinant proteins. To make chimeric antibodies, genes expressing murine proteins are spliced into a myeloma (or some other expression system) to make a recombinant cell line.[41] The resulting immunoglobulin is mostly human, but features murine variable regions. Humanized antibodies are created with recombinant genes that express the peptide chains comprising just the complementarity determining region, only the active

---

[39] Karen G. Burnett, Julia P. Leung, and Joanne Martinis, "Human Monoclonal Antibodies to Defined Antigens: Toward Clinical Applications," pp. 113-133.

[40] Dayton T. Rearden, Claude F. Meares, David A. Goodwin, Maureen McTigue, Gary S. David, Mary R. Stone, Julia P. Leung, Richard M. Bartholomew, and James M. Frincke, "Antibodies against metal chelates," Nature 1983, 316: 265-268.

[41] Catherine B. Beidler, James R. Ludwig, Jose Cardenas, Julia Phelps, Carol G. Papworth, Evan Melcher, Michael Sierzega, Laura J. Myers, Barbara W. Unger, Mary Fisher, Gary S. David, and M. Jaqueline Johnson, "Cloning and high level expression of a chimeric antibody with specificity for human carcinoembryonic antigen," Journal of Immunology, 1988, 141, 11: 4053-4060.

antigen recognizing tips of a murine antibody.[42] Bifunctional antibodies are engineered to react with two different antigens simultaneously.[43] Recombinant immunoglobulins tend to have lower affinities for their antigenic targets than the murine antibodies from which they have borrowed genes, and, at the time, manufacturing them in large quantities was a struggle. Hybritech's protein engineers attempted to improve the binding characteristics of the antibodies, and they experimented with various production techniques. Hybritech's in vivo R&D program wasn't making much commercial or medical progress, but, as a scientific project, it was very productive.

BIG MONEY

Hybritech had begun, in 1978, as a free-wheeling, science-driven operation, and while it had been successful raising money, sustaining R&D operations was a significant financial drain. By the mid-1980s, Hybritech's "burn rate" was accelerating and the company was in a continual financial squeeze. Product development, manufacturing, and sales and marketing teams and infrastructures had been assembled as needs for these functions arose, and the company had recruited experienced, highly-qualified personnel from the diagnostics and pharmaceutical

---

[42] Chimeric antibodies are roughly one-third murine and two-thirds human. Humanized antibodies are about 5-10% mouse and 90-95% human.

[43] Julie L. Phelps, Daniel E. Beidler, Rodney A. Jue, Barbara W. Unger, and M. Jaqueline Johnson, "Expression and characterization of a chimeric bifunctional antibody with therapeutic applications," Journal of Immunology 1990, 145, 4: 1200-1204. Bifunctional antibodies can also be produced chemically. See Karen G. Burnett, Joanne Martinis, and Richard Bartholomew, "Production of Bifunctional Antibodies by Hybridoma Technology," pp. 401-409 in Biotechnology: Applications and Research, ed. Paul N. Cheremisinoff and Robert P. Ouellette, Lancaster, PA: Technomic, 1985; J. Martinis, J.F. Kull, G. Franz, and R.M. Bartholomew, "Monoclonal antibodies with dual specificity," Protides of the Biological Fluids Vol. 30, 1982: 311-316.

industries to put these operations into place. Still, transforming Hybritech from a house of research into a manufacturer and marketer of clinical medical products had been accomplished only gradually over several years, and not without growing pains and episodes of financial crisis. There was never enough money, and effectively allocating and monitoring resources in a rapidly growing and evolving organization was a difficult task, and one that Hybritech had yet to master.

The company had gone public in 1981, garnering proceeds of $11 million,[44] and a secondary offering the following year yielded another $30 million,[45] but this was not enough to support the kinds of research programs that the company envisioned.[46] As a public company, much of Hybritech's value on Wall Street resided with the promise of hybridoma technology in cancer research. The company had performed well. It had become profitable midway through 1983 by manufacturing and marketing its in vitro diagnostic kits, but investors were still waiting on the development of in vivo imaging and therapeutic products. That was what Hybritech had advertised in its stock offerings, and that was where the big pay-off was expected. At the same time, the company could not afford to deplete its existing capital reserves on these projects. That would have meant balance sheet losses that Wall Street would surely have penalized.

---

[44] Hybritech, Inc., "Initial Public Stock Offering Prospectus," October 28, 1981.

[45] "Hybritech Inc. Offers Shares at $26.75 Each," Wall Street Journal, Thursday, Nov 11, 1982, p. 41.

[46] Conditions in the stock market dashed Hybritech's high hopes for its IPO. Genentech had gone public in October 1980 and had raised $35 million. Cetus went out in March 1981 and brought back $100 million. Both were firms were in Kleiner Perkins' portfolio. Hybritech rushed to follow on, but by the time the IPO was set to go, the market was, as Greene puts it, "in free fall." The company's take was disappointing. Greene felt that the company was worth much more.

Hybritech decided to raise money for cancer research by forming what was called an R&D partnership, a financing instrument that a number of biotech companies were exploiting at the time.[47] It was structured in this manner: investors in the partnership would receive intellectual property rights. Any downstream revenues generated by this property would be distributed in the form of royalties. In the meantime, contributions to the partnership qualified as tax write-offs. It was an attractive income shelter, and, provided one had faith in monoclonal antibodies, it could be considered a potentially lucrative investment.[48] Hybritech would be allowed to book the money raised in this way as both revenues and R&D expenditures, so in terms of profit and loss statements, the effect was neutral. The company could spend on R&D without endangering the price of its stock. Through Kleiner Perkins, among other links, Hybritech was keyed into the financial networks of the biotech community, and so was aware of this alternative. Genentech, another Kleiner Perkins company, had used this vehicle, and, it was discussed by the Hybritech board of directors. According to Kim Blickenstaff, a manager in Hybritech finance department, Tim Wollaeger, the firm's CFO, championed the approach: "Tim said, 'We need to do this. This is what we need to ramp the R&D, to go after the whole cancer area.' That was the idea, to ramp up the cancer diagnostics and therapeutics area." The program was called Hybritech Clinical Partners, and the company hoped to raise $80 million for cancer research.

---

[47] See "Limited Partnerships Fund Biotech Research," Chemical Week February 2, 1983: 55-56.

[48] This tax shelter was eliminated by the 1986 Tax Reform Act. Consequently, small, R&D-driven biotech companies became even more dependent on larger corporate partners.

Unlike public stock offerings, pieces of R&D partnerships had to be sold to high net worth individuals. Sales were to be conducted by Merrill Lynch, Shearson Lehman Brothers, and Dean Witter. The plan was for the Hybritech management team to go around the country for two weeks giving talks to brokers from each of these investment banks, who would then sell the idea to their clients. Merrill Lynch was the largest and they were leading the deal, so they decided to take Ted Greene, the CEO, to their meetings. He had the greater marquee value. Shearson Lehman was bigger than Dean Witter, so they chose David Hale, the president of the company. Tim Wollaeger, the CFO, went with Dean Witter. The response from the brokers and their clients was not overwhelming. After two weeks, the orders were tallied, and just over $7 million had been raised. Hybritech was in shock. In anticipation of this deal, the company had been rapidly expanding the payroll and had taken on an additional 80,000 square feet of building space. A potential disaster was brewing. The Hybritech executives concluded that the brokers simply did not know how to present the idea of monoclonal antibodies to investors in convincing fashion. Someone would have to step into the breach to make the deal work. Of the monies that had been raised, Dean Witter had delivered $5 million, so they were given the lead role, and it was decided by the board and the Hybritech management team that Tim Wollaeger should go back on the road to assist brokers from each of the banks. Blickenstaff gives his appraisal of the situation and the response of Hybritech's senior management:

> In the early days of the roadshow, I think they thought it was going to be these big institutions, hit them in twenty-one days, boom, close the deal and you're off, but it went on for months. I think people just lost

> interest after they found out it was a retail deal and that's the way it was going to be sold. I think some of the senior people just didn't have the time. Tim sort of single-handedly scraped up the garbage and got the troops moving again.

Wollaeger put together a slide presentation that explained monoclonal antibodies and Hybritech's plans to use them to develop cancer diagnostics and therapeutics. He then flew back and forth across the country meeting with brokers and small groups of their clients (and for this particular offering, most were physicians). After some early successes, the brokers began to report to their colleagues that they had written up orders, had high rates of participation from their customers, and had earned nice commissions on their sales. Wollaeger recalls that he was soon booked solid:

> I spent the next five months giving my presentation almost every day: breakfast, lunch, and dinner, breakfast, lunch, and dinner, breakfast, lunch and dinner. I'd never been able to sleep on an airplane before, but I'd just hear the engines start and conk out. I'd give a breakfast meeting in Minneapolis, lunch in Chicago, dinner in Detroit, fly at night, and start out in Philadelphia, Wilmington, Washington, D.C., the next day. I was just all over the place. I went to Alaska. We ended up with something like 1300 investors and I met 1200 of them.

Today, on the wall of Wollaeger's office hangs a plaque; on it is a map of the United States criss-crossed by lines indicating the miles he traveled by air during this time. At the bottom is a figure indicating the amount of money that he raised for Hybritech Clinical Partners: $70 million.[49] Blickenstaff remembers that this influx of capital radically altered the complexion of the company: "Immediately, we had the freedom to spend all this money on R&D, and we launched on building facilities and hiring people. You couldn't keep track of all the people coming in the door. It had a

huge impact. It completely changed the company." Hybritech kept getting bigger and bigger. The company had enough money to fuel its expansion for a while, but it wouldn't last long. Almost immediately, questions arose about where the next the sum would be found, and how the firm would spin its pitch for investors.

In October of 1984, just months after the partnership placement had closed, Eli Lilly began to make overtures to Hybritech about the purchase of the company.[50] Given the company's insatiable appetite for cash, along with competitive and legal troubles that the firm had encountered,[51] and the realities of the drug development process that had become painfully apparent to everyone at Hybritech, if not yet to investors, the board of directors decided to listen. Cole Owen reports that, "There was a lot of discussion, and some disagreement on the Hybritech side, internally. Should we do the deal? Was it too soon? Were we still growing in value?" David Kabakoff,

---

[49] "Hybritech Completes $70 million Placement," Wall Street Journal, Monday, July 30, 1984, p. 23.

[50] Serious discussions and negotiations, however, did not get underway until another nine months had passed. Eli Lilly and Company was founded in Indianapolis, Indiana in 1876, and maintained its standing as a leading developer and manufacturer of pharmaceuticals through the 20th century. In 1984, Lilly employed 28,000 people and generated revenues in excess of $3 billion. Lilly coveted Hybritech's know how in hybridoma technology and monoclonal antibodies. The company wanted to broaden its access to new biotechnologies. It had already licensed, manufactured, and marketed Genentech's recombinant human insulin.

[51] In March of 1984, Hybritech sued Monoclonal Antibodies, Inc., of Mountain View, CA, for infringement of the TANDEM patent in federal court. In August of 1985, the court ruled in favor of the defendant, and declared the patent invalid, holding that the substitution of monoclonal antibodies in existing immunoassay designs constituted an obvious step to those practiced in the art. See U.S. District Court, Northern District, California, Hybritech v. Monoclonal Antibodies, Inc., #C-81-0930, August 28, 1985. The ruling was overturned on appeal in September 1986. The Court of Appeals decided that, as Gary David had testified at the original trial, it was "obvious to try" to incorporate monoclonal antibodies into immunoassays, but not obvious how to succeed. Hybritech maintained that the novelty of the invention derived from the skillful application of hybridoma technology. The TANDEM assay, on this view, did not represent a straightforward substitution of monoclonal antibodies for polyclonal antibodies, but resulted from experimentation with hybridoma technology. See Hybritech Incorporated v. Monoclonal Antibodies, Inc., Appeal No. 86-531, United States Court of Appeals for the Federal Circuit, September 19, 1986. The company was also tangled up in expensive legal proceedings with Abbott.

vice-president of diagnostics R&D heard the same talk: "There was a lot of controversy at the board. It was not a unanimous view that the company should be sold. There was one very large shareholder, though, who wanted to liquidate their position, and that was a very catalytic event." [52]

It had been Ted Greene's dream to build an independent, fully integrated pharmaceutical company, but he knew that Hybritech's financial situation remained insecure. Everyone knew it. Owen says, "It was clear that we had to have more money. We were at the point where we had to do another financing." Ivor Royston maintains that the board, after reviewing the circumstances of the company and its R&D programs, was unanimous in its opinion that a serious run at pharmaceutical development, "was going to take a lot more money." Greene was forced to admit, "Our business plan didn't come out as we envisioned."[53] The directors finally determined that a sale to a large corporation like Lilly would be the preferred means of meeting obligations to shareholders and sustaining existing R&D projects in the long-term. The event would have enormous implications for the future of San Diego biotechnology.

---

[52] Kabakoff is referring to Henry Hillman. At the time of the sale, Hillman controlled 25.4% of Hybritech, and an unspecified portion of an additional 30.8%. See Hybritech Proxy Statement-Sale Prospectus, February 14, 1986. Reportedly, Hillman had floated the idea of a merger to his friend and colleague on the board of Chemical Back, Richard Wood, who happened also to be the chairman and CEO of Eli Lilly and Company. See Casey S. Opitz, "Eli Lilly and Company," Darden School Case UVA-F-0794, Charlottesville, VA: University of Virginia Darden School Foundation, 1988.

[53] Robert Teitelman, "Fatal Flaws?" Forbes, November 18, 1985; pp. 94, 99.

XI. PROFESSORS, PROFITS, PROGRESS, AND PROBLEMS

> Our civilization is characterized by the word 'progress.' Progress is its form rather than making progress being one of its features.
>
> Ludwig Wittgenstein

UNIVERSITY/INDUSTRY RELATIONS

Many recent social scientific studies of science and technology have focused on political, moral, and ethical problems surrounding the commercialization and application of biotechnologies. This study has not so far addressed such issues because in the Hybritech story, they rarely became salient practical concerns for involved parties. In this concluding chapter, I survey conflicts of interest and value associated with biotechnological development, and consider how the empirical findings of this study bear on efforts to understand them. The problems are complex. Since the late 1970s and early 1980s, many academic life scientists have become engaged in entrepreneurial activities beyond the ivory tower. Reviews of this spontaneous trafficking have been mixed. In addition to triggering intermittent flurries of financial speculation on Wall Street and generating optimistic attitudes among regional planners in certain parts of the world, this trend and the biotechnical advances that have appeared in its wake have stirred occasional controversies on college campuses and in many different public forums.

Institutional arrangements in the sciences are currently in a state of turbulent flux. University administrators, industrialists, and representatives of government at all levels are in the process of negotiating new social relationships and forms of cooperation in the hopes of spurring technological development in ways that will best

serve the interests of their own institutions and organizations and those of the public as well.[1] Many involved in these processes cite as reasons for pursuing new university-industry partnerships as aggressively and extensively as can be propitiously managed external pressures that can be traced ultimately to intensifying global economic competition. Academic bureaucrats promote and defend the implementation of new rules and programs facilitating the commercialization of research by pointing to transformations in national industrial policy and related shifts in federal funding priorities, strategems intended to enhance the nation's economic competitiveness. Lawmakers and other government officials now, more broadly and emphatically than ever before, identify the transfer of technologies from universities to the private sector as an essential ingredient in recipes for economic growth.[2] They wish to harness and utilize scientific techniques and labor power in ways that will contribute more

---

[1] See Association of American Universities, Trends in Technology Transfer at Universities: Report of the Clearinghouse on University-Industry Relations, Washington, D.C.: Association of American Universities; Henry Etzkowitz and Loet Leydesdorff, eds, Universities and the Global Knowledge Economy: A Triple Helix of University-Industry-Government Relations, London: Pinter, 1997; Michael Gibbons, et al., eds., The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies, London: Sage, 1994; Karen Seashore Louis, et al., "Entrepreneurs in Academe: An Exploration of Behaviors Among Life Scientists," Administrative Science Quarterly, 1989, 34: 110-131.

[2] For broad articulations of this view at the federal level, see, for example, William J. Clinton and Albert Gore, Jr., Science in the National Interest, Washington, D.C.: Executive Office of the President, 1994; and Technology for American's Economic Growth: A New Direction to Build Economic Growth, Washington, D.C.: Executive Office of the President, 1993. These statements represent programmatic revisions of Vannevar Bush's 1945 blueprint for the national exploitation of scientific research in the postwar era, Science: The Endless Frontier: A Report to the President on a Program for Postwar Scientific Research, Washington, D.C.: National Science Foundation, 1960 [1945]. Bush advocated massive federal investments in basic science, and outlined mechanisms for administering them. A loosely coordinated infrastructure for supporting university-based research – one roughly in line with Bush's plan – was subsequently put into place. See Daniel Lee Kleinman, Politics on the Endless Frontier: Postwar Research Policy in the United States, Durham, NC: Duke University Press, 1995. The Clinton Administration addressed the role of science and technology in the new 'globalized,' 'post-industrial,' 'knowledge-based' economy.

effectively to processes of technological development in industrial settings, and to the generation of greater wealth in local, regional, and national economies.[3]

The key piece of legislation that paved the way for more extensive university-industry interactions was the Bayh-Dole Act passed in 1980.[4] This law permitted universities and other academic research institutions to retain intellectual property rights to research funded by the federal government, thus providing financial incentives for academic collaborations with industry. The purpose of the legislation was, in essence, to install a decentralized system of technology transfer that would outperform government efforts restricted by commitments to non-exclusive licensing. Recent policy changes have aimed to streamline flows of scientific knowledge and inventions to industry, where they can be converted more efficiently into technological innovations, not by altering substantially the role of the government, but rather by encouraging the reconstruction of institutional interfaces between the academy and the private sector.[5]

---

[3] Henry Etzkowitz, "From Zero-Sum to Value-Added Strategies: The Emergence of Knowledge-Based Industrial Policy in the States of the United States," Policy Studies Journal, 1997, 25, 3: 412-424; Irwin Feller, "Federal and State Governmental Roles in Science and Technology," Economic Development Quarterly, 1997, 11, 4: 283-295; Karen M. Paget, "State Government-University Cooperation," pp. 344-380 in Growth Policy in the Age of High Technology, eds. Jurgen Schmandt and Robert Wilson, Boston: Unwin Hyman, 1990.

[4] David R. Mowery and Arvidis Zeidonis, "Academic Patent Quality and Quantity Before and After the Bayh-Dole Act in the United States," Research Policy, 2002, 31, 3: 399-418; David C. Mowery, Richard Nelson, Bhaven N. Sampat, and Arvidis Zeidonis, "The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980," Research Policy 2001, 30, 1: 99-119; Richard R. Nelson, "Observations on the Post Bayh-Dole Rise of Patenting at American Universities," Journal of Technology Transfer, 2001, 26, 1/2: 13-19.

[5] Wesley M. Cohen, Richard R. Nelson and John P. Walsh, "Links and Impacts: The Influence of Public Research on Industrial R&D," Management Science, 2002, 48, 1: 1-23; Maryann Feldman, Irwin Feller, Janet Berkovits, and Richard Burton, "Equity and Technology Transfer Strategies at American Research Universities," Management Science 2002, 48, 1: 105-121; David C. Mowery, Bhaven N. Sampat, Arvidis A. Ziedonis, "Learning to Patent: Institutional Experience, Learning, and the

Universities have, in large measure, accepted their new roles as engines of economic progress.[6] Within the framework of this expanded mission, they have begun to explore new schemes for securing financial support that will augment public funding for scientific inquiry in the future.[7] Although academic institutions stand to benefit materially from closer and more extensive ties with the private sector, this swing toward the 'corporatization' of science has not been unanimously applauded. American universities have been patenting discoveries, licensing intellectual properties, and consigning technologies to industry since universities began to assume their modern forms and institutional roles in the late 19th century (although, until

---

Characteristics of U.S. University Patents after the Bayh-Dole Act, 1981-1992," Management Science, 2002, 48, 1: 73-89; David C. Mowery, Richard R. Nelson, and Bhaven Sampat, et al., "The Growth of Patenting and Licensing by U.S. Universities: An Assessment of the Effects of the Bayh-Dole Act of 1980," Research Policy, 2001, 30, 1: 99-119; Jason Owen-Smith, "Dockets, Deals, and Sagas: Commensuration and the Rationalization of Experience in University Licensing," Social Studies of Science, forthcoming, 2004; Jason Owen-Smith, "Trends and Transitions in the Institutional Environment of Public and Private Science," Journal of Higher Education, forthcoming, 2004; Jason Owen-Smith, "From Separate Systems to a Hybrid Order: Accumulative Advantage Across Public and Private Science at Research One Universities," Research Policy 2003, 32, 6: 1081-1104; Jason Owen-Smith, "New Arenas for Academic Competition: Accumulative Advantage and Stratification in University Patenting," pp. 23-54 in Degrees of Compromise: Industrial Interests and Academic Values, ed. Jennifer Croissant and Sal Restivo, Albany, NY: SUNY Press, 2001; Jason Owen-Smith and Walter W. Powell, "The Expanding Role of University Patenting in the Life Sciences: Assessing the Importance of Experience and Connectivity," Research Policy 2003, 32, 9: 1695-1711; Jason Owen-Smith and Walter W. Powell, "To Patent or Not: Faculty Decisions and Institutional Success at Technology Transfer," Journal of Technology Transfer 2001, 26, 1: 99-114; Jerry Thursby and Marie Thursby, "Sources of Growth in University Licensing," Management Science 2002, 48, 1: 90-104.

[6] See, for example, University of California, Office of the President, Five Years of Progress – A Summary Report on the Results of the 1997 President's Retreat: The University of California's Relationships with Industry in Research and Technology Transfer, Oakland, CA: University of California, Office of the President, July 2002.

[7] Henry Etzkowitz and Lois Peters, "Profiting From Knowledge: Organizational Innovation and the Evolution of Academic Norms," Minerva, 1991, 29: 133-166; Michael J. Dooris, "Organizational Adaptation and the Commercialization of Research Universities," Planning for Higher Education, 1989, 17, 3: 21-31; James Fairweather, "Academic Research and Instruction: The Industrial Connection," Journal of Higher Education, 1989, 60, 4: 388-407; Walter W. Powell and Jason Owen-Smith, "Universities and the Market for Intellectual Property in the Life Sciences," Journal of Policy Analysis and Management, 1998, 17, 2: 253-277; Walter W. Powell and Jason Owen-Smith, "The New World of

recently, not those developed with federal monies). Ensuring that investments in scientific research are translated into practical benefits for the common good has long been accepted as one the university's basic functions and civic responsibilities.[8] Still, traditionalists respond by seeking to maintain the distance that has long separated basic science and the marketplace.

Despite scientists' perennial dissatisfaction with levels of federal support for basic research,[9] policy changes that have increasingly funneled research monies into 'applied' projects, and the growing acceptance of university-industry ties within the scientific community,[10] the proper means of commercializing academic research remains a heated issue.[11] Many scientists and other observers believe that relaxed

---

Knowledge Production in the Life Sciences," pp. 107-132 in The Future of the City of Intellect: The Changing American University, ed. Steven Brint, Stanford, CA: Stanford University Press, 2002.

[8] See Henry Etzkowitz, "Enterprises from Science: The Origins of Science-Based Regional Economic Development," Minerva, 1993, 31, 3: 326-360; Roger L. Geiger, To Advance Knowledge: The Growth of American Research Universities, Oxford University Press, 1986; Charles Weiner, "Patenting and Academic Research: Historical Case Studies," Science, Technology & Human Values, 1987, 12, 1: 50-62; Richard Whitley, The Intellectual and Social Organization of the Sciences, Oxford: Clarendon, 1984.

[9] See Daniel S. Greenberg, "Congress, Can You Spare a Grant?" Lancet, 2 March 1991, 337: 542-543.

[10] See Yong S. Lee, "'Technology Transfer' and the Research University: A Search for the Boundaries of University-Industry Collaboration," Research Policy 1996, 25: 843-863. Lee's survey of university faculty indicates a pronounced shift in attitudes in favor of active university participation in the commercialization of knowledge. However, a majority of researchers apparently continue to oppose direct university-industry partnerships. For additional information on researchers' attitudes, see Dianne Rahm, "Academic Perceptions of University-Firm Technology Transfer," Policy Studies Journal, 1994, 22: 267-278; and David BenDaniel, Kristina Szafara, and Prem Shukla, "What Aspects of the Culture of Technical Professors and the Structure of Research Universities Help or Hinder the Transfer of Technology to Start-Up Ventures?" n.d., Center for Entrepreneurial Leadership, Ewing Marion Kauffman Foundation, and Johnson Graduate School of Management, Cornell University.

[11] The issue has sparked institutional research in many different fields – law, history, economics, sociology, philosophy, and others. Many audiences want to be informed about the practical organizational and economic consequences and the legal and ethical implications of recent changes (including scientists, students, businesspeople, university administrators, politicians, judges, medical patients, consumers, investors, stock analysts, and so on).

approaches toward the oversight of arrangements in which university faculty conduct industry-sponsored contract research, participate actively in industrial projects, or accept equity positions in private ventures may have deleterious consequences for academic institutions and the 'purity' of science.[12] The escalating privatization of research, they contend, may generate unacceptable conflicts of interest and commitment,[13] promote secrecy and inhibit open communication within scientific communities,[14] unduly influence the direction of research agendas,[15] and encourage scientific fraud, theft, and other forms of misconduct.[16]

---

[12] For an historical examination of changes in academic-industrial relations, see Sheldon Krimsky, Science in the Public Interest: Has the Lure of Profits Corrupted Biomedical Research?, Lanham, MD: Rowman & Littlefield, 2003.

[13] These issues are examined from various perspectives by Rebecca Eisenberg, "Proprietary Rights and the Norms of Science in Biotechnology Research," Yale Law Journal, 97 (1987): 177-231; Henry Etzkowitz, "Conflicts of Interest and Commitment in Academic Science in the United States," Minerva, 1996, 34: 259-277; Henry Etzkowitz and Andrew Webster, "Science as Intellectual Property," pp. 480-505 in Handbook of Science and Technology Studies, eds., Sheila Jasanoff, et al., Thousand Oaks, CA: Sage, 1995; Roger J. Porter and Thomas E. Malone, eds., Biomedical Research: Collaboration and Conflict of Interest, Baltimore, MD: Johns Hopkins University Press, 1992; Paula Samuelson, "Innovation and Competition: Conflicts Over Intellectual Property Rights in New Technology," Science, Technology & Human Values, 1987, 9: 6-21; Charles Weiner, "Universities, Professors, and Patents: A Continuing Controversy," Technology Review, 1986 (February-March): 33-43.

[14] Nicholas Argyres and Julia P. Liebeskind, "Privatizing the Intellectual Commons: Universities and the Commercialization of Biotechnology Research," Journal of Economic Behavior and Organizations, 1998, 35: 427-454; David Blumenthal, et al., "Withholding of Research Results in Academic Life Science: Evidence from a National Survey of Faculty," Journal of the American Medical Association, 1997, 277: 1224-1228; Michael Gibbons and Bjorn Wittrock, eds., Science as a Commodity: Threats to the Open Community of Scholars, Harlow, Essex, UK: Longman, 1985; Michael Mackenzie, Peter Keating, and Alberto Cambrosio, "Patents and Free Scientific Information in Biotechnology: Making Monoclonal Antibodies Proprietary," Science, Technology & Human Values, 1990, 15, 1: 65-83; Rebecca S. Eisenberg and Richard R. Nelson, "Public vs. Proprietary Science: A Fruitful Tension?" Daedalus, 2002, 131, 2: 89-102; Michael A. Heller and Rebecca S. Eisenberg, "Can Patents Deter Innovation? The Anticommons of Biomedical Research," Science, 1998, 280, 5364: 698-701; Julia Porter Liebeskind and Amalya L. Oliver, "From Handshake to Contract: Trust, Intellectual Property and the Social Structure of Academic Research," pp. 118-145 in Trust Within and Between Organizations, eds. Cristel Land and Reinhard Bachmann, Oxford: Oxford University Press, 1998; K.W. McCain, "Communication, Competition, and Secrecy: The Production and Dissemination of Research-Related Information in Genetics," Science, Technology & Human Values, 1991, 16: 491-516; Steven A. Rosenberg, "Secrecy in Medical Research," New England Journal of Medicine, 1996, 334, 6: 392-394; Miriam Solomon, "Information and the Ethics of Information Control in Science," Perspectives on Science, 1996, 4, 2: 195-206.

On similar grounds, critics of new arrangements argue that when university administrations enter into formal commercial partnerships with industry or establish private ventures in order to capitalize on research conducted within their institutions, they overstep their mandate to deliver practical goods and promote economic development,[17] and act to undermine the traditional educational mission and independent station of the university in modern society.[18] At stake in these disputes

---

[15] Eric G. Campbell, et al., "Looking a Gift Horse in the Mouth: Corporate Gifts Supporting Life Science Research," Journal of the American Medical Association, 1998, 297, 113: 995; Andrew Webster, "University-Corporate Ties and the Construction of Research Agendas," Sociology, 1994, 28, 1: 123-142; John Ziman, "The Problem of 'Problem Choice,'" Minerva, 1987, 25: 92-106.

[16] See Barbara Mishkin, "Misconduct: Regulating and Investigating Scientific Reseach," pp. 183-190 in Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century, eds. Frederick B. Rudolph and Larry V. McIntire, Washington, D.C.: Joseph Henry Press, 1996; National Academy of Sciences (Panel on Scientific Responsibility and the Conduct of Research; Committee on Science, Engineering, and Public Policy), National Academy of Engineering, and Institute of Medicine, Responsible Science: Ensuring the Integrity of the Research Process, Vol. 2, Washington, D.C.: National Academy Press, 1993.

[17] See, for example, David Dickson, The New Politics of Science, Chicago: University of Chicago Press, 1984, ch. 1-2; Daniel S. Greenberg, Science, Money, and Politics: Political Triumph and Ethical Erosion, Chicago and London: University of Chicago Press, 2001; Nicholas Wade, The Science Business, New York: Priority, 1984.

[18] For a range of opinions on these institutional transformations, see Derek C. Bok, Universities in the Marketplace: The Commercialization of Higher Education, Princeton, NJ: Princeton University Press, 2003, and Universities and the Future of America, Durham, NC: Duke University Press, 1990; Norman E. Bowie, University-Business Partnerships: An Assessment, Lanham, MD: Rowman & Littlefield, 1994; Eric Gould, The University in a Corporate Culture, New Haven, CT: Yale University Press, 2003; Clark Kerr, The Uses of the University, Cambridge, MA: Harvard University Press, 1995; Corynne McSherry, Who Owns Academic Work? Battling for Control of Intellectual Property, Cambridge, MA: Harvard University Press, 2001; Bernard D. Reams, Jr., University-Industry Research Partnerships: The Major Legal Issues in Research and Development Agreements, Westport, CT: Quorum, 1986; Frank H.T. Rhodes, The Creation of the Future: The Role of the American University, Ithaca, NY: Cornell University Press, 2001; Nathan Rosenberg and Richard R. Nelson, American Universities and Technical Advance in Industry, Stanford, CA: Center for Economic Policy Research, Stanford University, 1993; James B. Rule, "Biotechnology: Big Money Comes to the University," Dissent, 1988, 53, 4: 430-436; Sheila Slaughter, The Higher Learning and High Technology: Dynamics of Higher Education Policy Formation, Albany, NY: State University of New York Press, 1990; Sheila Slaughter and Larry L. Leslie, Academic Capitalism: Politics, Policies, and the Entrepreneurial University, Baltimore, MD: Johns Hopkins University Press, 1997; Andrew Webster and Kathryn Packer, eds., Innovation and the Intellectual Property System, London: Kluwer Law International, 1996; Mary Lindenstein Walshok, Knowledge Without Boundaries: What America's Research Universities Can Do for the Economy, the Workplace, and the Community, San Francisco: Jossey-Bass, 1995.

are different visions of the social roles and obligations of persons and institutions involved in the production and dissemination of scientific knowledge, different visions of how the sciences can and should contribute to the larger society that supports and sustains them.

Insofar as the life sciences are concerned, however, the recent trend that finds universities and academic researchers increasingly involved in industry did not appear initially as the result of any broadly coordinated effort to design and implement new models of research and development. It took shape, instead, as many localized happenings – entrepreneurial actions, informal collaborations, and the implementation of university-industry alliances on a case-by-case basis in order to solve contingent problems and further the ends of specific academic institutions and corporate entities.[19] In describing this organic process, social scientists Dorothy Nelkin, Richard Nelson, and Casey Kiernan observe that "all institutions have a tendency toward parochialism." They note, however, that "the total effect of many incremental changes is not necessarily small."[20] Attempts to harmonize protocols and formulate general guidelines for this kind of institutional restructuring have proved controversial. Settling on the 'correct' means of advancing science and industry together entails, not

---

[19] For empirical research on the scope and magnitude of recent changes, see David Blumenthal, "Academic-Industry Relationships in the Life Sciences: Extent, Consequences, and Management," Journal of the American Medical Association, 1992, 268, 23: 3344-3349; David Blumenthal, et al., "Participation of Life Science Faculty in Research Relationships with Industry," New England Journal of Medicine, 1996, 335, 23: 1734-1739; Wesley M. Cohen, Richard Florida, and W.R. Roe, University-Industry Research Centers in the United States, Pittsburgh, PA: Carnegie Mellon University Press, 1994; Gary Matkin, Technology Transfer and the University, New York: Macmillan, 1990; David Roessner and Anne Wise, "Public Policy and Emerging Sources of Technology and Technical Information," Policy Studies Journal, 1994, 22, 2: 349-358.

[20] Dorothy Nelkin and Richard Nelson, with the assistance of Casey Kiernan, "Commentary: University-Industry Alliances," Science, Technology & Human Values, 1987, 12, 1: 65-74.

only negotiating accords among those pursuing localized practical agendas, but also defining broader institutional purposes, and defining public interests as well. All such formulations are, of course, contested.[21] As university administrators, scientists, government agencies, and industrialists attempt to plot courses of action and paths of research in this uncertain environment, debates on how to proceed have sometimes become polarized.

THE NORMATIVE STRUCTURE OF SCIENCE

This is so, in part at least, because deliberations are often framed – and rarely usefully – in terms of abstract values and philosophical principle. In the social sciences, analysts seeking to inform or influence policy formation routinely preface reports on the implications of recent changes by referencing sociologist Robert K. Merton's famous account of special "scientific norms" said to underwrite the autonomy of the scientific community.[22] Merton articulated a set of values and rules of conduct, an ethos, to which, he asserted, members of the scientific community are held strictly accountable. This he summed up in four interrelated principles: 1) universalism, "the canon that truth-claims, whatever their source, are to be subjected to preestablished impersonal criteria;" 2) communism (or "communalism," as Merton later rephrased it), the idea that "the scientist's claim to 'his' intellectual 'property' is limited to that of recognition and esteem;" 3) disinterestedness, the notion that science

---

[21] See Gary Rhoades and Sheila Slaughter, "Professors, Administrators, and Patents: The Negotiation of Technology Transfer," Sociology of Education, 1991, 64: 65-77.

[22] Robert K. Merton, "The Normative Structure of Science," pp. 267-278 in The Sociology of Science: Theoretical and Empirical Investigations, ed. Norman Storer, Chicago: University of Chicago Press, 1973.

consists in the pursuit of knowledge for its own sake, above all other ends; and 4) organized skepticism, the collective commitment to the "detached scrutiny of beliefs," regardless of the social authority that forwards them.[23] Merton believed that when scientific work and systems of reward are organized in ways that adhere faithfully to these values and rules, the rational confirmation of scientific knowledge claims is guaranteed (eventually, if not immediately in every instance). On this view, objective knowledge is institutionally manufactured: while competition among scientists generates "incentives for eclipsing rivals by illicit means...such impulses can find scant opportunity for expression in the field of scientific research."[24] This is so, Merton declared, because "...the activities of scientists are subject to rigorous policing to a degree perhaps unparalleled in any other field of activity."[25]

In the sociology of science, there has lately been a massive reevaluation of the 'Mertonian paradigm.' Since Merton published his essay on scientific norms in 1942, he and many followers have attempted to refine its portrayal of scientific practice, to produce a model with greater empirical adequacy. Several additional norms have been identified and incorporated into Merton's general analytic framework, including originality, humility, rationality, and individualism.[26] However, as empirical findings have accumulated, and as the model has become ever more complex, it has become

---

[23] Merton, "The Normative Structure of Science," pp. 270-278.

[24] Merton, "The Normative Structure of Science," p. 276.

[25] Merton, "The Normative Structure of Science," p. 276.

[26] See, for example, Robert K. Merton, "Behavior Patterns of Scientists," pp. 325-342, and "The Ambivalence of Scientists," pp. 383-418 in The Sociology of Science: Theoretical and Empirical Investigations, ed. Norman Storer, Chicago: University of Chicago Press, 1973.

increasingly difficult for Mertonians to defend the basic assumption of their approach – that there is, in fact, a stable and coherent normative structure that characterizes 'good science.' Ethnographic and historical studies of scientific practice have shown that reliable knowledge is often produced in the breach of the 'scientific ethos,' late amendments notwithstanding,[27] and further, that scientific knowledge claims are not subject to any extraordinary scrutiny.[28] Scientific communities have their own conventional ways of generating, evaluating, and representing knowledge, but the codes of conduct to which scientists are bound are no more onerous or strictly administered than those to which others professionals are routinely expected to conform, and perhaps, in some cases, less so. In the sociology of science, the claim has been retracted that scientific communities are free of the run-of-the-mill imperfections that characterize other social establishments. Few, if any, social scientists will nowadays defend literal readings of the Mertonian account.

Neither will many involved in academic policy-making accept analyses that contrast the recent emergence of the life science business with idealized portraits of

---

[27] For an empirical demonstration, see Ian Mitroff, "Norms and Counter-Norms in a Select Group of Apollo Moon Scientists: A Case Study of the Ambivalence of Scientists," American Sociological Review, 1974, 39: 579-595. For each of the principal norms posited by Merton (universalism, disinterestedness, communalism, and organized skepticism), Mitroff identified the pull, in his case study, of opposing values (particularism, self-interestedness, solitariness, and organized dogmatism).

[28] Mertonians have asserted that the replicability of experimental findings is the cornerstone of scientific objectivity. See, for example, Harriet Zuckerman, "Deviant Behavior and Social Control in Science," pp. 87-138 in Deviance and Social Change, ed. Edward Sagarin, Beverly Hills, CA: Sage, 1977. It is by reproducing experiments, they contend, that scientists skeptically, impartially, and collectively check up on each other and verify knowledge claims. Against this assumption, H.M. Collins points out that in the course of routine scientific work "replication of others' findings and results is an activity that is rarely practised." Only in extraordinary circumstances is the validity of knowledge assessed in this manner. Further, Collins has shown that the replication of experiments depends on prior social agreements about what will count as evidence of reproducibility. In other words, the practical meanings of scientific norms are forever negotiable. See H.M. Collins, Changing Order: Replication and Induction in Scientific Practice, Chicago: University of Chicago Press, [1985] 1991, p. 19, and ch. 2.

the scientific community as realistic assessments of problems now confronting universities. Nearly all concede that the sciences are inescapably subject to economic and political influences. Still, many attempting to get to grips with the complex problems attending contemporary bioscientific research continue to cling to qualified versions of scientific exceptionalism, arguing that scientific institutions can and should be distinguished by standards of behavior that uphold the core values of Merton's ethos. The norms of disinterestedness and communalism are here understood as ideals to be emulated if never fully realized.[29] Although acknowledged to be flawed as empirical descriptions of actual scientific practice, they are said to serve an important prescriptive function as a "cultural myth."[30] Robert M. Rosenzweig proposes that even if this myth does not adequately depict the realities of scientific work, it nevertheless reminds scientists of "how they ought to behave."[31] From this

---

[29] A few scientists remain firmly committed to scientific ideals in their 'pure' forms. See, for example, Cèsar Milstein, "Patents on Scientific Discoveries Are Unfair and Potentially Dangerous," The Scientist, November 1, 1993: 11. Some lay observers lobbying against the privatization of scientific knowledge are wont to make use of 'ivory tower' rhetoric, as well. Journalist Robert Bazell, for example, refers to the participation of academic life scientists in the commercialization of biotechnical inventions as "a virus" that threatens the objectivity of science. See Robert Bazell, "Virus: Science and Society – Biomedical Scientists, Universities, and Commercial Conflicts of Interest," New Republic, 9 November 1992: 21-22. Science writer Linda Marsa likewise claims that "...the quest for profits has poisoned science.... [t]he scientific culture is now so steeped in business that research is governed by the whims of the marketplace, not by good science." See Linda Marsa, "Prescriptions for Profits: How the Pharmaceutical Industry Bankrolled the Unholy Marriage Between Science and Business," New York: Scribner, 1997, p. 7. Bazell and Marsa are plainly wedded to the notion that science consists in the disinterested pursuit of truth, and so, is essentially antithetical to the interested pursuit of profit. Selflessly advancing knowledge, on this view, is the duty of the scientist. The integrity of the scientific enterprise depends on the degree to which individuals and institutions embrace this duty and forgo opportunities for private gain.

[30] For an account of the theoretical logic underlying such interpretations, see Michael Lynch, Scientific Practice and Ordinary Action: Ethnomethodology and Social Studies of Science, Cambridge: Cambridge University Press, 1993, pp. 59-67.

[31] Robert M. Rosenzweig, "Research as Intellectual Property: Influences Within the University," Science, Technology & Human Values, 1985, 10: 41-48. See also Judith P. Swazey, "Ensuring the

perspective, present uncertainties about the propriety of commercializing research are read as signs of potential institutional disintegration. The problem is not one of defining values, for these are already given, but rather specifying what will count as misconduct in new boundary-spanning practices and relationships. Without such legislation, it is assumed, the integrity of science is at risk because it cannot be enforced. And, it is feared, public confidence in science may wane if research practices begin to stray too far from traditional ideals.

THE SPECIAL RELATIVITY OF SCIENTIFIC NORMS

Some social scientists spinning out relativistic variations on this theme focus on the rhetorical dimensions of such arguments. They conceptualize formal policy-making procedures within academic institutions as means of smoothing over discrepancies between mythical ideals and actual practices, as mechanisms for legitimating collective projects or modes of conduct that appear to be at odds with the values of disinterestedness and communalism. Accounts of scientific norms are interpreted here as professional or institutional ideologies, and enactments of formal rules are said to reflect practical material concerns. Such rules are taken to represent, not simple expressions of normative solidarity within scientific institutions, but negotiated settlements that align conflicting interests under the auspices of central administrations.

Henry Etzkowitz, for example, describes university policy-making on issues of commercialization as a process in which the meanings of established norms have been

---

Ethical Conduct of Research: Who is Responsible?" pp. 175-182 in Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century, Washington, D.C.: Joseph Henry Press, 1996.

reinterpreted in light of prevailing social and economic conditions to which scientific institutions and particular groups within them have been forced to adapt.[32] Rather than vigilantly guaranteeing that the participatory roles of universities and their faculties in commercial enterprises conform to traditional ideals and codes of conduct, policy-makers have produced, Etzkowitz maintains, "rationalizations to show how norms are not violated by new forms of behavior."[33] Typically, these rationalizations have invoked the obligations of scientists and scientific institutions to effect technology transfers in order to deliver economic benefits to the public. By translating institutional and professional interests into this more congenial vocabulary of justification, administrators attempt to ensure that "what had previously been seen as in conflict or incompatible with the proper ways of doing science is seen as in fact compatible."[34]

On Etzkowitz' view, recent changes in the sponsorship of biological research and the control of intellectual property represent clear departures from conventional

---

[32] Henry Etzkowitz, "Entrepreneurial Science in the Academy: A Case of the Transformation of Norms," Social Problems, 1989, 36, 1: 14-29; p. 27. Etzkowitz' approach resembles 'neoinstitutionalist theory' in the sociology of organizations (although Etzkowitz does not himself acknowledge this school of thought). For an explanation of 'neoinstitutionalism,' see John W. Meyer and Brian Rowan, "Institutionalized Organizations: Formal Structure as Myth and Ceremony," American Journal of Sociology, 1977, 83: 340-362. For a partial critique, see Gary Rhoades and Sheila Slaughter, "Professors, Administrators, and Patents: The Negotiation of Technology Transfer," Sociology of Education, 1991, 64: 65-77. Rhoades and Slaughter draw on "reproduction-resistance theory" for inspiration, crediting, among other works, Henry A. Giroux, Ideology, Culture, and the Process of Schooling, Philadelphia: Temple University Press, 1981. They emphasize internal organizational conflicts, criticize neoinstitutionalists for neglecting them, and view university policies as outcomes of struggles for organizational control (in this case, conflicts between faculty and administrators regarding the conditions and rewards of technical work). For a broadly similar argument forwarded from within the Mertonian school, see Thomas F. Gieryn, "Boundary-Work and The Demarcation of Science and Non-Science," American Sociological Review, 1983, 48: 781-795. The presuppositions that underlie these various approaches were earlier articulated by Michael J. Mulkay, "Norms and Ideology in Science," Social Science Information, 1976, 15: 637-656.

[33] Etzkowitz, "Entrepreneurial Science in the Academy," pp. 26-27.

practices within the academy and from once settled relationships between universities and the private sector. They are not, however, understood as instances of deviance nor indications of normlessness. Etzkowitz decribes them, instead, as moments in a broader process of cultural change, a "transformation of norms" that permits universities to authorize forays into private enterprise. He considers formal adjustments of scientific ideologies to be "surface manifestations of underlying changes in the organization of research." They comprise the "final phase" of an institutional response to extrinsic economic and political pressures.[35] Etzkowitz rightly identifies the strategic intent of these sorts of 'legitimation processes,' and the functional significance of rules that reallocate rights to the ownership of intellectual properties. But the suggestion that formal protocols somehow reflect the actual normative character of organizations or institutions is problematic. As Etzkowitz himself notes, university policy-making has lagged behind the concrete implementation of new social arrangements. This historical fact begs questions about just where, when, and how official rationalizations come to bear on situated practices.

There is a basic analytic confusion embedded in Etzkowitz' account. He employs material conditions and interests as explanatory constructs, yet assumes that subsequently transformed norms exert some more or less pervasive governing force on individuals and groups within academic institutions, resolving contradictions and repairing inconsistencies among abstract values and concrete practices that have been induced by 'external pressures.' Etzkowitz continues to emphasize formal rules as

---

[34] Etzkowitz, "Entrepreneurial Science in the Academy," p. 26.

[35] Etzkowitz, "Entrepreneurial Science in the Academy," p. 27.

codified expressions of the full range of normative expectations within an institution, while simultaneously explaining how revisions of established codes were prompted and shaped by individuals and groups taking advantage of unsanctioned opportunities for profit. In reporting that the 'initial' reaction of a molecular biologist to the changing environment in the academy ("I never realized I had a trade.... I can do good science and make money") followed administrative efforts to "encourage faculty to see their work in new, economically relevant ways," he implies that practical opportunities were largely created by official dicta.[36] The normative character of prior entrepreneurial initiatives is never specified. Opportunity structures for professorial enterprise have certainly been transformed by administrative rescriptions, and the implementation of rules that explicitly indicate the propriety and merit of an activity may well motivate persons to engage in it,[37] but, of course, many molecular biologists did not wait on university committees to reinterpret the 'scientific ethos' before starting companies and moving into the private sector. They struck out on their own within existing frameworks of administrative control.

Accounts like Etzkowitz' that depict the recent commercialization of biological research as an institutional reponse to outlying shifts in regional, national, and global political economies tend to gloss over the spontaneous character of entrepreneurship

---

[36] Etzkowitz, "Entrepreneurial Science in the Academy," p. 26.

[37] Of recent changes in the occupational roles of university faculty members, the availability of resources for starting companies, and collegial attitudes regarding contact and involvement with the private sector, one professor says: "If the culture encourages it, people will do it." See David BenDaniel, Kristina Szafara, and Prem Shukla, "What Aspects of the Culture of Technical Professors and the Structure of Research Universities Help or Hinder the Transfer of Technology to Start-Up Ventures?" Center for Entrepreneurial Leadership, Ewing Marion Kauffman Foundation, and Johnson Graduate School of Management, Cornell University, n.d.; p. 7.

and the ways in which individuals operating independently, apart from institutionally prescribed roles and obligations, initially sparked this episode of social change. Etzkowitz nods at the historical significance of academics' entrepreneurial actions, but the theoretical status of such undertakings in his story of normative change is unclear. These activities preceded the formulation of new university rules and agendas that have since officially validated them. Apparently, then, they are to be listed among the 'external pressures' that have altered practices in research universities and the life sciences from without.

Discussing events and influences that occasioned the enactment of new patenting policies at a major university in 1981, Etzkowitz cites changes in federal law, but also includes the nationwide publicity that attended the intitial offering of stock in Genentech in October 1980. Genentech, founded in 1976, in the San Francisco Bay Area, was the first dedicated biotechnology company to appear on the scene, and the first to go public. The firm's IPO revealed "the origins of the company's technology in the laboratories of California academics," and made clear to university administrators "the potential financial opportunities in academic research."[38] Etzkowitz reports that:

> Media coverage of investors clamoring to participate in the Genentech stock offering and the stock's sharp rise in price on the initial day of public trading gave new salience to a scientific field that had only a few years earlier been an arcane area of academic interest. The molecular revolution in biology, largely supported by government funding, had made it possible for a venture capitalist, a professor, and their associates to become millionaires. Biotechnology now promised to become a generator of immense wealth, at least in the imaginations of

[38] Etzkowitz, "Entrepreneurial Science in the Academy," p. 19.

> administrators and academics newly attuned to capital markets. University administrators hoped to capture for their institutions some of the wealth that had in the case of Genentech accrued to a faculty member and venture capitalist. Some faculty came to view Professor Boyer as a model; if he could start a firm, so could they.[39]

As Etzkowitz relates, the Genentech IPO was a momentous event in the history of the biotechnology industry. The dollars that poured into the company's coffers on that autumn day had an enormous impact on subsequent happenings both within academic institutions and elsewhere.[40] However, major research universities had for some time been exploring new avenues of technology transfer through the formation of private ventures and partnerships with industry.[41] And by 1980, the wave of entrepreneurial start-ups that established the field of commercial biotechnology was already well underway. University faculty had by then secured millions in venture capital, started dozens of companies, and managed successfully to negotiate the transfer of technologies in accordance with existing protocols.[42] Some had accepted

---

[39] Etzkowitz, "Entrepreneurial Science in the Academy," p. 19. Herbert Boyer was a University of California, San Francisco biochemist who, in 1973, in collaboration with Stanley Cohen, a Stanford molecular biologist, first developed recombinant DNA techniques. The pair manipulated the expression of proteins in E. coli bacteria by inserting into their genes pieces of foreign DNA. The venture capitalist Etzkowitz refers to was Robert Swanson, who teamed with Boyer to start Genentech. He served as the company's chairman until December 1996. See Ralph T. King, Jr., "Genentech's Robert Swanson, A Pioneer of Biotechnology, to Retire as Chairman," Wall Street Journal, 13 December, 1996: B12. Cohen did not become directly involved in the operation of the firm.

[40] Martin Kenney also points to the Genentech IPO as a turning point, not necessarily for administrators, but for individual life scientists. The offering, in Kenney's view, had a corrosive effect on the bioscience community. He contends that professors were, in 1977 and 1978, "reluctant to join to companies because of peer pressure," but began to abandon traditional values when prospects of riches became palpable: "...Genentech's success in attracting capital and the clear indications that Boyer would soon be rich began to change minds." See Kenney, Biotechnology, p. 96.

[41] See Kenney, Biotechnology, ch. 2-4.

[42] Lee and Burrill report that 105 new biotechnology companies were founded between 1976 and 1980. See Kenneth B. Lee, Jr., and G. Steven Burrill, Biotech '96: Pursuing Sustainability, An Industry Annual Report, Palo Alto, CA: Ernst & Young, LLP, 1995. Kenney concludes that, at least as far as new ventures utilizing rDNA techniques were concerned, "the startup window was from 1978 to 1980."

equity positions and duties as officers and board members in these new ventures, and many more had agreed to render services as paid consultants.[43] They sometimes endured snubs from colleagues for doing so, but they did not, generally speaking, run afoul of university rules. Scientists or administrators critical of commercial activities could cite no chapter or verse that would equate profit-seeking or profit-making with misconduct.

Even many scientists who declined to capitalize on their own research remained circumspect when commenting on the propriety of entrepreneurial venturing by their colleagues. For example, in 1977, Paul Berg, a Stanford Nobel Laureate in biochemistry who reportedly abjured any personal connection with industry, said of the Genentech venture: "Commercial involvement is just not to my taste. This isn't to criticize Herb [Boyer] particularly, but I just can't see it."[44] Framing the issue as a matter of personal preference or choice – and Berg, for one, was apparently reluctant to do otherwise, at least when speaking publicly – casts doubt on the notion that any broadly shared antipathies toward the interested pursuit of personal gain or activities that might compromise the organizational autonomy of universities ever constituted regulative norms within scientific disciplines.

See Kenney, Biotechnology: The University-Industry Complex, p. 172, n16. The subsequent development of new technologies gave rise to later surges in start-up activity, but gene-splicing tools made their way from academic labs to industry for the most part before university policy-makers moved either to encourage or to regulate this kind of activity.

[43] See Kenney, Biotechnology: The University-Industry Complex, ch. 5-7.

[44] C. Petit, "The Bold Entrepreneurs of Genetic Engineering," San Francisco Chronicle, 1977, December 2: 1.

The mixing of business and science in the development of biotechnologies initially prompted many bioresearchers to express misgivings. Typically, rationales for these conservative positions appealed to sentiments regarding the purity of science. Some scientists still give voice to such concerns and personal convictions. While broad changes in attitudes regarding the propriety of academic entrepreneurship have apparently occurred, the weight of opinion has yet to produce a normative consensus.[45] And as long as individual scientists continue to hold conflicting views on the issue, then such a resolution can be effected only by imposing stricter administrative controls on university-based research. This is, of course, something that few involved in present debates consider a viable alternative. Given this circumstance, if analysts insist on gauging the integrity or character of the sciences by the degree to which they are directed exclusively toward the formally stated ends of academic institutions, then the manifest absence of a consensus in the responses of scientists to the commercialization of biological research in the late 1970s and early 1980s has to be interpreted as a sign of massive corruption. Similarly, if the growth of disinterested knowledge and the manufacture of valuable commodities and means of production are genuinely incompatible activities, then attempts by university administrators to integrate both objectives into institutional agendas must be treated as symptoms of systemic disorder.

---

[45] See Jason Owen-Smith and Walter W. Powell, "Careers and Contradictions: Faculty Responses to the Transformation of Knowledge and Its Uses in the Life Sciences," pp. 109-140 in Research in the Sociology of Work, vol. 10; The Transformation of Work, ed. Steven P. Vallas, Amsterdam: JAI Press, 2001; and Daniel Lee Kleinman and Steven Peter Vallas, "Science, Capitalism, and the Rise of the 'Knowledge Worker': The Changing Structure of Knowledge Production in the United States," Theory and Society, 2001, 30, 4: 451-492.

Etzkowitz' attempt to avoid the horns of this dilemma by referring to a 'transformation of norms,' a shift in the value orientations of scientists and university administrations from principled disapproval of involvement with industry to principled support for such activity fails on both logical and empirical grounds. On the one hand, his interpretation implies that separate administrative jurisdictions in the academy, the corporate world, and government mark definite boundaries between 'science' and 'nonscience' (i.e., an 'external' domain that includes business, the economy, and politics), the contours of which can be located, at any given point in time, by comparing the normative expectations that distinguish one side of this division from the other. On the other hand, he maintains that, within the bailiwick of science, these expectations are subject to revision and change, and, further, that events on the 'outside' have influenced the formation of values on the 'inside.' The explanation that Etzkowitz builds on these contradictory assumptions is, in addition, confounded by the fact that scientific entrepreneurs have, in the course of transferring intellectual properties and scientific skills from the academy to industry, operated in both spheres simultaneously without committing clear-cut violations of rules in either, and by the fact that many traditionalists continue to object nonetheless.

WITTGENSTEIN AND THE SOCIOLOGY OF SCIENTIFIC KNOWLEDGE

There is another sociological approach to conceptualizing the rules and values of scientific work that manages to dissolve these explanatory conundrums. I adopt it here to analyze the commercialization of biotechologies in San Diego. The British sociology of scientific knowledge (described above in chapter one, pp. 57-74) was developed, in part, as a reaction to the 'Mertonian paradigm.' Drawing on studies of

ordinary language use, and in particular, the philosophy of Ludwig Wittgenstein,[46] its adherents have produced empirically grounded descriptions of the ways in which rules of inquiry and personal conduct in the sciences are construed and observed in actual practice. In this approach, conformity with a norm is not understood as the application of an abstract principle to a particular situation putatively 'covered' by it. The rationale for this position is rooted in the following assumption, borrowed from Wittgenstein, and offered here by Michael Mulkay: "no rule can specify completely what is to count as following or not following that rule."[47] If this is allowed, it becomes apparent that any attempt to specify a general rule for interpreting another opens the door to an infinite regress of interpretive trouble.

This simple point has far-reaching implications for sociological inquiry generally, and, naturally, for social studies of scientific methods and rules of conduct, too. According to sociologists of scientific knowledge, cognitive and social norms must be inferred from practical routines, conventional patterns of action that characterize particular scientific settings. The mores of science are said to be embedded in these organizational practices. Empirical inquiries have shown that the meanings of formal statements of method or professional ethics are context-bound, determined by social processes of negotiation and interpretation in definite concrete

[46] For general discussions of the application of Wittgenstein's ideas in social studies of science, see David Bloor, Wittgenstein: A Social Theory of Knowledge, New York: Columbia University Press, 1983; and Michael Lynch, Scientific Practice and Ordinary Action: Ethnomethodological and Social Studies of Science, Cambridge: Cambridge University Press, 1993, ch. 2-3.

[47] Michael J. Mulkay, "Interpretation and the Use of Rules: The Case of the Norms of Science," pp. 111-125 in Science and Social Structure: A Festschrift for Robert K. Merton, ed. Thomas F. Gieryn, Transactions of the New York Academy of Sciences, Series II, vol. 49; p. 111.

circumstances.[48] The actual 'rules' used to evaluate modes of action in such settings are found to be largely tacit, and far more complex, fluid, and dependent on situational contingencies than accounts of 'normative structures' can adequately portray.

Studies in the sociology of scientific knowledge are not concerned with determining the extent to which concrete practices conform to normative ideals. Rather, they attempt to document how normative expectations and vocabularies and rubrics of evaluation are generated, sustained, applied, and transformed in actual practice. In the case of formally articulated rules, the aim is not to investigate how such prescriptions are followed, but, instead, how they are mobilized by individuals and groups as they attempt to identify and respond to situated actions as instances of appropriate or inappropriate behavior. The maintenance of scientific values is thus understood as an open-ended social process in which conventional practices, sanctioned both formally and informally, emerge as adaptive solutions to localized problems of order. From this perspective, then, the values and maxims of organization that characterize the sciences cannot be encapsulated in overarching statements of abstract principle. Attempts to formulate such statements misrepresent the normative character of science. They incorporate into accounts basic misunderstandings about

---

[48] By interpretation, I do not mean to indicate a systematic decision procedure. Practitioners are not ordinarily required to choose among conflicting interpretations in either typical or novel situations because, for the most part, the contextual meanings of rules are established and made self-evident in the course of practical interaction. Only in extraordinary circumstances, when practical agreements break down, do people find it necessary to specify relationships between formal rules and situated actions. See David Bloor, "Left and Right Wittgensteinians," pp. 266-282 in Science as Practice and Culture, ed. Andrew Pickering, Chicago: University of Chicago Press, 1992; and Michael Lynch, "Extending Wittgenstein: The Pivotal Move from Epistemology to the Sociology of Science," pp. 215-265, and "From the Will to Theory to the Discursive Collage: A Reply to Bloor's 'Left and Right Wittgensteinians,'" pp. 283-300 in Science as Practice and Culture, ed. Andrew Pickering, Chicago: University of Chicago Press, 1992.

what it means to follow a rule, to make sense, to execute a procedure correctly, or to behave in an ethically sound manner.

In contrast to the Mertonian view, the sociology of scientific knowledge does not start from the notion that 'good science,' or distinctions between 'pure' and 'applied' science, can be defined by general evaluative criteria. As Barry Barnes and David Edge explain, "...such judgments cannot ever be decisively and unproblematically justified, by objective or rational means: they are endemically contingent."[49] Empirical investigations in the sociology of scientific knowledge are not dictated by these categories. Instead, researchers take up the rhetorical and political or ideological creation and maintenance of such classifications as topics of inquiry. The actual boundaries of scientific and technical communities are determined by mapping concrete associations, which may, in practice, extend across formal institutional domains. And because the patterns of interaction that comprise these communities are recognized to be existentially determined and subject to revision, either within the confines of established organizations or through the formation of innovative links across traditional boundaries, sociologists of scientific knowledge maintain that academic institutions are characterized by an ineliminable normative uncertainty.[50] Bodies of reliable scientific knowledge and advances in technological capacities are generated by experts who retain the authority to make independent

---

[49] Barry Barnes and David Edge, "The Organization of Academic Science: Communication and Control," pp. 13-20 in Science in Context: Readings in the Sociology of Science, eds. Barry Barnes and David Edge, Milton Keynes: Open University Press, 1982, p. 18.

[50] For various opinions on the implications of this view for science studies, see Peter Galison and David J. Stump, The Disunity of Science: Boundaries, Contexts, and Power, Stanford, CA: Stanford University Press, 1996.

judgments, at least insofar as the regulation of the technical and local organizational aspects of their work are concerned. Consequently, as Barnes and Edge observe, "the associated normative questions of how expert knowledge is best assessed, and how experts themselves are best evaluated and kept under a modicum of control, raise such intractable and viciously circular problems as to strangle speech."[51] University administrators, then, if they wish to foster innovation and technical progress in the sciences, are obliged to tolerate conditions of normative indeterminacy as enduring facts of institutional life.

The sociology of scientific knowledge has examined critically the empirical grounds of Mertonian claims that scientific institutions are exceptional, and rejected the idea that the normative and epistemological dimensions of scientific practice are of a special kind. This has cleared the way for investigations into the ways in which scientific activities are organized and carried out in concrete practice. To recognize that scientific institutions are not houses of special virtue is not to question the objectivity or reliability of scientific knowledge, nor to question that scientists working within these institutions are committed to producing objective, reliable knowledge. It is, however, an excuse for reopening investigations into just how, and in what kinds of organizational arrangements, these commitments are sustained. Modern social institutions generally do not impose totalizing forms of discipline, or demand from participants exclusive allegiances to their formally stated purposes. Academic institutions, as studies of scientific knowledge production have shown, are

---

[51] Barry Barnes and David Edge, "General Introduction," pp. 1-12 in Science in Context: Readings in the Sociology of Science, eds. Barry Barnes and David Edge, Milton Keynes: Open University Press, 1982, p. 11.

not special cases in this regard. If they were, their capacities for generating technical advances would be correspondingly restricted.

ABIDING BY THE RULES IN SAN DIEGO

The growth of the biotech industry in San Diego over the past twenty-five years has been facilitated by the formation of new kinds of relationships among life scientists, institutions of academic research, and private business ventures. The city's principal scientific institutions – UCSD, Salk, and Scripps – have each begun actively to pursue licensing agreements, cooperative research partnerships, and other technology transfer, resource exchange, and funding arrangements with commercial firms, large and small, in the pharmaceutical and diagnostics industries.[52] Consequently, the conditions, and the character, too, of biological research in San

[52] The University of California has numerous organs that facilitate cooperation and exchanges with industry, including the Office of Technology Transfer, the Industry-University Cooperative Research Program (IUCRP), and the California Institutes for Science and Innovation. The San Diego campus, like the other nine in the statewide system, has its own local offices that promote university-industry connections. These include the Office of Technology Transfer and Intellectual Property Services, for example, that operates more or less independently within the parameters of general UC policy, and negotiates its own deals. There is UCSD Connect, too, a university extension office that works to foster high-tech entrepreneurship in San Diego, and to hasten and smooth the way for the commercialization of UCSD technologies. The office organizes meetings, for example, that bring faculty entrepreneurs together with venture capitalists, and start-ups together with larger corporate partners. Several academic schools and departments at the university maintain their own outreach programs, as well. The UCSD Division of Biological Sciences has established an arm called BioCore, and the Department of Chemistry and Biochemistry houses an Industrial Relations Office. These programs put industry personnel into university classrooms and laboratories, they place students in internships, and graduates in jobs, and they assist in the administration of collaborative research ventures between university bioscientists and corporate affiliates. A number of research units that stand on campus without undergraduate teaching missions – the Institute for Biomedical Engineering, for instance – also work closely with commercial firms on development projects. In 1997, the university took an unprecedented step when it entered into a joint commercial venture with the German diagnostics corporation, Boehringer Mannheim (which was subsequently acquired by Roche). The company, called Molecular Medicine, LLC, was set up to provide contract research and manufacturing services to biological laboratories. Managed by the UCSD School of Medicine's gene therapy program, it specialized in the production of gene therapy reagents (e.g., viral vectors). UCSD's intent was to raise capital and provide operating support for the clinical applications laboratory of the gene therapy program. In 2001, the company was purchased by Molecular Medicine Bioservices, Inc.

Diego have been significantly altered. In San Diego, as elsewhere, the academic life sciences are now supported increasingly by – in addition to grants from the government and private foundations – monies flowing from industry in the form of gifts, endowments, direct research funding, and fees for licenses and services. Further, the involvement of academic bioscientists in commercial operations as consultants, contract researchers, or entrepreneurs is today common and widely accepted. Not all observers have been pleased with these trends, but supporters have far outnumbered detractors. Academic administrators and life scientists, city government officials, and members of San Diego's business community have generally approved, and the public at large has not voiced any sustained objections. Minor controversies have occasionally been sparked by exchanges of information, materials, personnel, and money across the academic-industrial divide, but none has prevented ties among the city's academics and industrialists from becoming ever stronger and more extensive over time. The reconfiguration of San Diego's life science community has proceeded smoothly, for the most part.

This innovative process was not spurred by big science or big business. It was initiated by individual scientific entrepreneurs. In the late 1970s, entrepreneurial scientists in the city began to create, with assistance from venture capitalists, a novel form of scientific organization – the biotech start-up firm. As they did, they established an entrepreneurial culture in and around San Diego's big houses of science (just as a handful of contemporaries were doing in a few other locales around the country and the world). Only then did formal administrative responses from academic institutions – i.e., new, expanded, or refined policies and procedures – and informal

reactions from the local research community, both positive and negative, begin to appear.[53] From the very beginning of the process, activities involving Hybritech, the first entrepreneurial biotech company on the local scene, helped to define relations between UCSD, Salk, Scripps, various other academic research organizations, and the commercial biotech industry as it took root and grew in the city.

For example, when Ivor Royston and Howard Birndorf founded Hybritech, they were able to transfer myeloma cells necessary for making hybridomas from UCSD to the new company without documenting the university's 'donation' (if the university did, in fact, own the cells – property rights were never claimed or tested). Royston's immediate superiors were perhaps aware that the cells existed, but probably very few others in the institution were. In any case, soon after Hybritech and then other start-ups began demonstrating the economic value of the biological materials with which they worked, the University of California and its academic neighbors in San Diego, along with sister institutions in other centers of biotech development, began to insist that their faculties maintain greater control over lab inventories, and they began to demand monetary compensation for materials stored on their premises. No longer would bioscientific resources be shared collegially without administrative monitoring and oversight – materials used for research purposes came to be treated as commodities or economic assets.[54]

---

[53] For a formal response, see, for example, University of California, Office of the President, "Interim Guidelines on University-Industry Relations," issued November 3, 1982.

[54] University of California, Office of the President, Guideline #10, "Tangible Research Products," Guidelines on University-Industry Relations, May 17th, 1989; University of California, Office of the President, "Interim Guidelines on University-Industry Relations," issued November 3, 1982.

By and large, San Diego's research institutions handled intellectual property, technology transfer, and faculty participation matters related to new biotech firms without a great deal of fanfare or administrative ado. In many instances, they adapted existing policies and procedures to the new circumstances and associations of bioscientists, and were satisfied that, in doing so, they had protected their economic interests and preserved their commitments to traditional academic missions. On occasion, however, situations without clear precedents emerged, and debates ensued among the academics about whether and how existing rules could be extended to cover them. Sometimes progressive faculty and administrators decided that existing protocols were inadequate and that innovative solutions would be required; conservative factions sometimes balked. When uncertainties emerged in this manner, pioneering scientific entrepreneurs often found themselves in the middle of policy scrums. Ivor Royston, for example, was involved in several flaps concerning his involvement in industrial projects and his work with monoclonal antibodies. After co-founding Hybritech and Idec, he elected to stay at his academic post, but he remained involved with both companies as a director, consultant, and sponsored researcher. Suspended in this way between academia and industry, he became a lightning rod for controversy, and, on several occasions, his activities provoked disapproval from colleagues and supervisors. The disputes in which Royston became embroiled at UCSD concerned the ownership of academic research products and conflicts of interest and commitment in researchers' affiliations with industry. It is worthwhile to consider his experiences – they illustrate how ethical and legal issues related to new arrangements in the life sciences were sorted out on the ground, in practice.

Once hybridomas and monoclonal antibodies became recognized as objects of medical and commercial value, academic institutions began to keep track of their whereabouts. In March of 1981, Royston and other colleagues at UCSD applied to patent a process for creating hybridomas of human origin by performing fusions with cells from a human lymphoblastoid B cell line instead of murine myeloma cells.[55] They knew that the hybridomas might be useful for therapeutic purposes, so, following established institutional protocols, they informed the university and let the administration decide whether it wanted to protect this piece of intellectual property. In this instance, the university – well aware of Royston's business success with Hybritech – decided to shoulder the substantial costs of obtaining the patent on the hybrids. Over the next several years, the researchers used the line to develop human monoclonal antibodies against various cancers, and published the results of their work in a long string of experimental and methodological papers.[56]

---

[55] Ivor Royston, Harold Handley, J. Edwin Seegmiller, and Linda F. Thompson, "Immunoglobulin-secreting human hybridomas from a cultured human lymphoblastoid cell line," U.S. Patent 4,451,570; filed March 26, 1981; issued May 29, 1984.

[56] H.H. Handley and I. Royston, "A human lymphoblastoid B cell line useful for generating immunoglobulin-secreting human-human hybridomas," pp. 125-132 in Hybridomas in Cancer Diagnosis and Treatment, eds., M. Mitchell and H. Oettgen, New York: Raven Press, 1982; M.C. Glassy, H.H. Handley, P.H. Cleveland, and I. Royston, "An enzyme immunofiltration assay useful for detecting human monoclonal antibody," Journal of Immunological Methods 58, 1983: 119-126; M.C. Glassy, H.H. Handley, D.H. Lowe, and I. Royston, "Human monoclonal antibodies to human cancers," pp, 163-170 in Monoclonal Antibodies and Cancer, eds. R.E. Langman, I.S. Trowbridge, and R. Dulbecco, San Diego: Academic Press, 1983; H.H. Handley, I. Royston, and M.C. Glassy, "The production of human monoclonal antibodies to human tumor associated antigens," pp. 617-620 in 15th International Leucocyte Culture Conference, eds. J.W. Park and R.L. O'Brien, New York: Wiley Interscience, 1984; D.H. Lowe, H.H. Handley, J. Schmidt, I. Royston, and M.C. Glassy, "A human monoclonal antibody reactive with human prostate," Journal of Urology 131, 1984: 780-785; M.C. Glassy, H.H. Handley, and I. Royston, "Design and production of human monoclonal antibodies immunoreactive with human cancers," pp. 211-225 in Human Hybridomas and Monoclonal Antibodies, eds. E.G. Engleman, S. Foung, R. Larrick, and A. Raubitscheck, New York: Plenum Publishing, 1985; M.C. Glassy, S.A. Gaffar, R.E. Peters, and I. Royston, "Human monoclonal antibodies to human cancer cells," pp. 97-109 in Monoclonal Antibodies and Cancer Therapy, eds. R.A. Reisfeld and S. Sell, New York: Liss, 1985; S.A. Gaffar, I. Royston, and M.C. Glassy, "Strategies for the design and use of

Human antibodies were attractive to Royston and his colleagues because they were perceived to hold some promise as immunotherapies for cancer. Unlike murine antibodies, human immunoglobulins don't produce 'HAMA' immune responses – the generation of human anti-mouse antibodies – when injected into patients. Murine antibodies were poor candidates for therapeutic applications because patients' HAMA reactions attempted to neutralize and clear them rapidly from the body before they could reach their targets. It had been established that they were suitable for in vivo diagnostic imaging because initial doses usually elicited only weak immune responses, and most of the immunoglobulins were able to make their antigenic connections. Treatment regimens, however, required multiple infusions of antisera. Repeated administrations typically led to increasing anti-mouse immunoglobulin titers and deteriorating conditions in the blood for the therapeutic antibodies, along with greater chances for adverse effects including hypersensitive allergic reactions. The UCSD researchers anticipated that human antibodies could be engineered in ways that would obviate these problems.

In the early 1980s, human monoclonals were prized commodities. Cell biologists had managed to produce a few specimens for expository purposes, but they remained difficult to manufacture. When Royston began exploring ways to cultivate human immunoglobulins that were useful for specific therapeutic purposes, no dependable method had been described in the scientific literature. Human

---

tumor-reactive human monoclonal antibodies," BioEssays 4, 1986: 119-123; M.C. Glassy, S.A. Gaffar, R.E. Peters, and I. Royston, "Immortalization of the human immune response to human cancer," pp. 205-225 in Human Hybridomas: Diagnostic and Therapeutic Applications, ed. Anthony J. Strelkauskaus, New York: Marcel Dekke, 1987.

lymphocyte/murine myeloma hybrids were not reliable sources of human antibodies because they were genetically unstable. They tended to eliminate human chromosomes and to lose their ability to secrete human immunoglobulins. There were a few human myeloma cell lines available, but they were notoriously uncooperative in the laboratory, and did not make good substitutes for murine myelomas in cell fusions. Human cells of all kinds are generally difficult to culture and they perform relatively poorly in the hybridization process. Royston's group, however, discovered a lymphoblastoid B cell line that worked consistently. They called it UC 729-6. Cells from the UC 729-6 line were hardy, grew rapidly, and fused well with both normal and malignant human B lymphocytes. In 1983, an independent review of immortalizing human cell lines published in the Journal of Immunology ranked UC 729-6 as the best available.[57]

The other fusion partners in the UCSD process were ordinary antibody-secreting human B lymphocytes (or sometimes human lymphoma or leukemia cells). Unlike the murine splenocytes used in conventional hybridoma techniques, however, these cells were not activated by prior immunizations.[58] Previous studies in the immunological and oncological literatures, confirmed by results of clinical investigations at UCSD, had shown that while human beings do not generally mount significant immune responses against cancers, B lymphocytes in cancer patients are

---

[57] P.G. Abrams, J.A. Knost, G. Clarke, S. Wilburn, R.K. Oldham, and K.A. Foon, "Determination of the optimal human cell lines for development of human hybridomas," Journal of Immunology 131, 1983: 1202.

[58] Ethical constraints on the immunization of human subjects make it difficult for researchers to obtain B lymphocytes producing antibodies to specific antigens. Royston's method was limited mainly to the manufacture of anti-cancer hybridomas.

nonetheless primed to generate antibodies against cancer cell surface antigens.[59] The lymphocytes used for fusions at UCSD were taken from the lymph nodes of cancer patients that drained regions around tumors. Monoclonal antibodies secreted by the resulting hybridomas did react with cancer cells – some with antigenic determinants characterizing a specific form of cancer, and some with antigens found across range of different tumor types. The UCSD researchers hoped that experimentation with these antibodies in the laboratory and the clinic would teach them how malignancies evade detection and attack by the immune system, and, perhaps, how new kinds of immunotherapy might be developed. (Studies in this line of work did, in fact, lead Royston to the production of the tumor-specific antibodies and anti-idiotype antibodies against B-cell lymphomas that became important legs of Idec's original technology platform).[60]

A dispute about the ownership of human hybridomas and their immunoglobulin products arose during the course of this research, in 1982, when Hideaki Hagiwara, a post-doc from Japan working in the UCSD biology department, approached Royston about the possibility of learning how to make human monoclonal antibodies in his laboratory. Hagiwara's mother in Japan was suffering from metastatic cervical cancer. Hagiwara proposed that he travel back home in order to

---

[59] J. Schlom, D. Wunderlich, and Y.A. Teramoto, "Generation of human monoclonal antibodies reactive with human mammary carcinoma cells," Proceedings of the National Academy of Sciences 77. 1980: 6841; D.H. Lowe, H.H. Handley, J. Schmidt, I. Royston, and M.C. Glassy, "A human monoclonal antibody reactive with prostate cancer," Journal of Urology 132, 1984: 780.

[60] Royston and his co-investigators observed that "UC 729-6 can be used to rescue Ig from nonsecretory malignant B cells and thereby allow for the production of anti-idiotype antibodies." See M.C. Glassy, H.H. Handley, H. Hagiwara, and I. Royston, "UC 729-6, a human lymphoblastoid cell line useful for generating antibody-secreting human-human hybridomas," Proceedings of the National Academy of Sciences 80, 1983: 6327-6331.

obtain tumor and lymph specimens from his mother for use as research materials. Royston agreed to take in the tissues, attempt to make antibodies against the cervical cancer, and let Hagiwara participate in the research. No written agreements were drawn up. Hagiwara went home to Japan, the biopsies were conducted, and he returned to UCSD with the samples. B cells from the lymph were fused with UC 729-6. Two of the resulting hybridomas, designated CLNH5 and CLNH11, produced functional monoclonal antibodies and were selected for further study. The CLNH5 antibody, an immunoglobulin of the IgM class, was especially interesting for Royston because it reacted with several human malignancies – to an antigen (or antigens) found on lung, prostate, and blood cancer cells in addition to the cervical cancer of Hagiwara's mother.[61]

Without the consent of Royston or the University of California, Hagiwara took CLNH5 and CLNH11 hybridomas back to Japan in order to treat his mother, hoping that the administration of monoclonals would stimulate a cell-mediated immune response against the tumors. Royston believes it was a medical landmark, the first in vivo use of a monoclonal serotherapy. The results were never reported. Mrs. Hagiwara later died, reportedly due to causes unrelated to her cancer.[62] The case was complicated by the fact that Hagiwara's father was a bioscientist and the director of the Hagiwara Institute of Health in Japan. The family possessed the means to

---

[61] M.C. Glassy, H.H. Handley, H. Hagiwara, and I. Royston, "UC 729-6, a human lymphoblastoid cell line useful for generating antibody-secreting human-human hybridomas," Proceedings of the National Academy of Sciences 80, 1983: 6327-6331.

[62] Warren Froelich, "Cancer 'Bullet' Researchers Win $1.8 Million Grant," San Diego Union, August 21, 1984.

manufacture large quantities of antibody. When the university learned of the situation, it asserted its ownership and patent rights. An agreement was reached that permitted the Hagiwaras to use the cells and antibodies for medical and scientific purposes on the condition that they would not commercialize the materials or the technology. Later, however, the Hagiwaras amended their position. They claimed co-ownership of the hybridomas because the immortalized hybrid cells propogated Mrs. Hagiwara's genes and gene products (i.e., the antibody proteins). However, Royston says, "neither side was anxious to spend a great deal of time and money in litigation over a cell line of questionable significance."[63] The case was settled when the university granted the Hagiwaras an exclusive license for use of the technology in Asia, and the Hagiwaras agreed to pay royalties to the university on the sales of any products.

University counsel Allen B. Wagner acknowledged that there was no obvious answer to the question of ownership (which remained unresolved in principle): "I am not able to tell you that the law in the case of Royston and Hagiwara is as clear as one would hope. In fact, it seems as though rapid movement in biomedical science has again outstripped the law's ability to keep up, so we're going to have to re-examine what we have."[64] Royston adopted a pragmatic approach to the policy dilemma. He advised that existing rules for protecting human subjects and determining the status of 'discarded tissues' provided sufficient guidance in most cases. He also recommended

---

[63] Ivor Royston, "Cell Lines from Human Patients: Who Owns Them?" Clinical Research, 33, 4, 1985: 442-443.

[64] Allen B. Wagner, "The Legal Impact of Patient Materials Used for Product Development in the Biomedical Industry," Clinical Research 33, 4, 1985: 444-447.

that researchers be excused from time-consuming meetings with attorneys and university officials when existing rules did not suffice:

> Until new laws are passed I approach these issues from a...practical point of view by distinguishing between the anonymous patient and the non-anonymous patient. When the patient is not known to the investigator and not concerned with the type of research that will use his discarded tissues the current consent form appears to be adequate. However, when the patient or the family is cognizant of the kind of research being done with his or her tissues, especially when there is direct investigator-subject interaction, and when there is a potential for a commercial product to result from the research, the current consent form may need to be supplemented with an agreement allowing the patient to waive his rights to such commercial products. If the patient does not wish to waive his rights I would have to ask the University to negotiate an agreement with him so that my time will not be taken up in subsequent litigation.[65]

Another incident involving Royston and proprietary control of monoclonal antibodies illustrates how the commercialization of biotechnologies transformed laboratory life in places like San Diego. When Royston moved from Stanford to UCSD and set up his laboratory in the La Jolla VA Hospital, he hired a student named John Majda as a lab assistant. Birndorf taught Majda how to make hybridomas and monoclonal antibodies, and Majda was present when the general partners of Kleiner-Perkins visited the laboratory to meet Royston and Birndorf and learn about cell hybridization. When Birndorf departed to found Hybritech in October 1978, Majda stayed on and continued to assist in Royston's laboratory. He eventually married Royston's secretary and left to attend medical school, but while he was at the lab, he helped Royston develop an antibody, T101, that Royston used for many years to differentiate T and B cells, and to identify and distinguish various cancers of the blood

and lymph.[66] T and B lymphocytes originate from the same stem cells. In terms of molecular surface structure, they bear many similarities. Royston's T101 antibody displayed an affinity for an antigen, now called CD5, found on normal and abnormal T cells, but not on most normal B cells.[67] It also bound to most chronic lymphocytic leukemia (CLL) cells, a cancer of B lymphocytes.[68] It did not bind to abnormal B cells exhibiting the characteristics of other proliferative B cell diseases, including lymphosarcoma cell leukemia (LCL), hairy cell leukemia (HCL), and various lymphomas. The evidence suggested that CLL is a malignancy of B cells occurring at an early stage of differentiation from the original stem cells that also give rise to T lymphocytes. Royston used the T101 antibody in many studies of the pathogenesis of

---

[65] Ivor Royston, "Cell Lines from Human Patients: Who Owns Them?" Clinical Research, 33, 4, 1985: 442-443.

[66] R. Taetle and I. Royston, "Human T-cell antigens defined by monoclonal antibodies. Absence of T65 on committed myeloid and erythroid progenitors," Blood 56, 5, 1980: 943-946; I. Royston, M.B. Omary, and I.S. Trowbridge, "Monoclonal antibodies to a human T-cell antigen and Ia-like antigen in the characterization of lymphoid leukemia," Transplantation Proceedings, 13, 1, 1981: 761-766; R.E. Sobol, R.O. Dillman, J.C. Beauregard, A.L. Yu, J.W. Lea, H. Collins, S. Wormsley, M.R. Green, R.R. Ellison, and I. Royston, "Clinical utility of monoclonal antibodies in the phenotyping of acute and chronic lymphocytic leukemia," pp. 417-425 in Protides of the Biological Fluids, Proceedings of the 30th Colloquium, ed. H. Peeters, Oxford: Pergamon Press, 1983; R.E. Sobol, I. Royston, T.W. LeBien, J. Minowada, K. Anderson, F.R. Davey, J. Cuttner, C. Schiffere, R.R. Ellison, and C.D. Bloomfield, "Adult acute lymphoblastic leukemia phenotypes defined by monoclonal antibodies," Blood 3, 1985: 730-735; D.L. Shawler, S.B. Wormsley, R.O. Dillman, D.M. Frisman, S.M. Baird, M.C. Glassy, and I. Royston, "The use of monoclonal antibodies and flow cytometry to detect peripheral blood and bone marrow involvement of a diffuse, poorly differentiated lymphoma," Journal of Immunopharmacology 7, 4, 1985: 423-432.

[67] It was later discovered that a small subset of B cells also display the CD5 molecule. For this reason, it turned out that monoclonal antibodies directed against other T cell antigens (CD3, CD4, and CD8) were better probes than T101. In the early 1980s, many academic and commercial laboratories were developing monoclonal antibodies to distinguish lymphocytes. Ortho, the diagnostics division of Johnson & Johnson, and Coulter manufactured anti-T cell antibodies for research and clinical testing purposes. Royston purchased and employed these products in his research, along with T101.

[68] I. Royston, J.A. Majda, S.M. Baird, B.L. Meserve, and J.C. Griffiths, "Human T cell antigens defined by monoclonal antibodies: The 65,000 dalton antigen of T cells (T65) is also found on chronic lymphocytic leukemia cells bearing surface immunoglobulin," Journal of Immunology 125, 2, 1980: 725-731. 1 to 3% of CLL cases are characterized by the proliferation of T cells and not B cells.

leukemias and lymphomas, and also as an experimental medical treatment of CLL, T cell leukemia, and Sezary syndrome, a cutaneous T-cell lymphoma.[69]

Majda helped to establish the T101-secreting hybridoma line in Royston's laboratory, and is credited on the patent as a co-inventor (along with Royston and Gayle Yamamoto, another lab technician).[70] The patent was assigned to the University of California. Hybritech licensed T101 from the university early in 1979, even before the patent application was filed, to develop as a research product for the differentiation of T and B cell subtypes, and, possibly, as a therapeutic for leukemia and lymphoma. In the third quarter of 1983, the company signed a research contract with the National Cancer Institute to develop medical applications of hybridoma technology, and to supply clinical investigators with antibodies and antibody-based therapeutics. The NCI wanted Hybritech to explore possibilities for using

---

[69] R.O. Dillman, R.E. Sobol, H. Collins, J. Beauregard, and I. Royston, "T101 monoclonal antibody therapy in chronic lymphocytic leukemia," pp. 151-171 in Hybridomas in Cancer Diagnosis and Treatment, eds. M.S. Mitchell and H.F. Oettgen, New York: Rave Press, 1982; R.O. Dillman, D.L. Shawler, R.E. Sobol, H.A. Collins, J.C. Beauregard, S.B. Wormsley, and I. Royston, "Murine monoclonal antibody therapy in two patients with chronic lymphocytic leukemia," Blood 5, 1982: 1036-1045; R.O. Dillman, J.C. Beauregard, D.L. Shawler, R.E. Sobol, and I. Royston, "Results of early trials using murine monoclonal antibodies in cancer therapy," pp. 353-358 in Protides of the Biological Fluids, Proceedings of the 30th Colloquium, ed. H. Peeters, Oxford: Pergamon Press, 1983; R.E. Sobol, R.O. Dillman, S. Halpern, D.L. Shawler, P. Hagan, S. Ferrone, M.C. Glassy, and I. Royston, "Serotherapy and radioimmunodetection of tumors with monoclonal antibodies," pp. 256-281 in Cellular Oncology: New Approaches in Biology, Diagnosis, and Treatment, Cancer Research Monographs, Vol. 1, eds. P.J. Moloy and G.L. Nicolson, New York: Praeger, 1983; R.O. Dillman, D.L. Shawler, J.B. Dillman, and I. Royston, "Therapy of chronic lymphocytic leukemia and cutaneous T-cell lymphoma with T101 monoclonal antibody," Journal of Clinical Oncology, 2, 8, 1984: 881-891; D.L. Shawler, M.C. Mitchell, S.B. Wormsley, I. Royston, and R.O. Dillman, "Induction of in vitro and in vivo antigenic modulation by the anti-human T cell monoclonal antibody T101," Cancer Research 44, 1984: 5921-5927; R.O. Dillman and I. Royston, "Applications of monoclonal antibodies in cancer therapy," British Medical Bulletin, 40, 3, 1984: 240-246; J.E. Leonard, Q. Wang, N.O. Kaplan, and I. Royston, "Kinetics of protein synthesis inactivation in human T-lymphocytes by selective monoclonal antibody-ricin conjugates," Cancer Research 45, 1985: 5263-5269.

[70] Ivor Royston, John Majda, and Gayle Yamamoto, "Monoclonal antibody methods and compositions specific for single antigens in antigen aggregates," U.S. Patent 4,675,386; filed November 27, 1979; continued May 19, 1983; issued June 23, 1987.

monoclonals as delivery vehicles for various anti-cancer chemotoxins, and to provide antibodies and coupling chemistries to clinicians conducting NCI-sponsored trials. The company did some of this, since the government was picking up the tab, but the Hybritech scientists all the while attempted to persuade their NCI colleagues to try monoclonal/radioisotope conjugates instead, for imaging and precision targeted radiation therapy. Gary David says: "They fought it for a while, but finally we convinced them to try putting some indium-labeled T101 into some CTCL [cutaneous T cell lymphoma] patients. They were flabbergasted. The results were so striking that suddenly they got interested in indium-labeled monoclonal antibodies, and then in ytrrium-labeled monoclonal antibodies."

So, Hybritech had T101 and was developing it clinically, with commercial applications in mind. Majda was a co-inventor, but he hadn't been informed about the arrangement between the university and the company. The property was UCSD's to handle as it saw fit, and the antibody hadn't yet generated any income. Until there were products and revenue streams, there were no royalties to distribute, rights to the invention had been handed over to the university, and the administration was under no obligation to keep Majda informed about property that it controlled. In 1980, however, Majda learned that Hybritech had the antibody and, according to Birndorf, made an appearance at the firm. Birndorf remembers it like this:

> He shows up one day at Hybritech with an attorney. He told us that he thought we had stolen things from the university, technology or cell lines. There was this one T-cell antibody that we were trying to work on, and we had a deal with the university about licensing it, or something, I don't remember, but he didn't know that. And basically, he threatened that he would go to the university and tell them if we

> didn't give him money. So we basically told him, 'Take your best shot,' you know?

No rules had been broken. Royston, as the faculty lab chief, had informed the university about the invention, the intellectual property, and the research materials, just as he was obliged to do. Hybritech had taken all of the proper steps to acquire the antibody. The technology and the cell line had been transferred in the manner prescribed by university policy. Still, Royston takes a sympathetic view of Majda's position:

> Given what happened later with Hybritech's success, he may have felt bitter that he was never cut into the whole thing, or didn't even get any stock in Hybritech, or whatever, because he probably felt that he was instrumental in the laboratory being successful and then us getting funded by Kleiner-Perkins. He may have felt cut out of this whole biotech revolution.

Unfortunately for Majda, T101 never made any money. No product ever came of it. In 1984, commercial rights to the antibody were assigned to Hybritech Clinical Partners, a limited research partnership set up by the company to fund in vivo diagnostics and therapeutics. In 1986, after the sale of Hybritech to Eli Lilly, Karen Klause was promoted and appointed president of the partnership. She subsequently elected not to develop T101 because the company had manufactured and in-licensed better antibodies for imaging and therapy. But Klause wouldn't release it to the NCI, either. Apparently, no agreement could be reached on royalty and liability terms. The NCI had hoped to take T101 to another company for development, but never had the chance. So, Majda never received a dime, and perhaps felt, as Royston suspects, that he was never properly recognized or compensated for his contribution to getting Hybritech off the ground in the first place. Royston says, generously – with respect to

scientific currency, that is: "It seems to me that, in discovery, or in any activity, there are always more people involved than there is credit to go around. There's always somebody who feels that they're not getting appropriate credit."[71] Birndorf comments on what has become routine in the life sciences since companies like Hybritech were founded and biotechnologies began to be recognized as things of substantial value: "It's funny, you know, when things are successful, people come back and they want all this money and stuff."

OUT OF THE FRYING PAN, INTO THE FIRE

In these controversies regarding the ownership of research materials and the observance of technology transfer protocols, Royston was involved in making accommodations and setting precedents that began to define academic-industrial relations in the context of the 'biotech revolution.' His direct involvement with Hybritech, as a consultant, board member, stock holder, and contract researcher, also raised policy questions regarding conflicts of interest and commitment. There was some confusion at the university, initially, about how to receive the news of Royston's entrepreneurial moonlighting. Many faculty on the scene at the time were not sure that it was allowed. Some were convinced that it should not be. Royston recalls:

---

[71] Birndorf isn't so magnanimous. He still holds a grudge, and revisiting the incident clearly doesn't bring out his best. He provides an epilogue to the Majda story: "About ten years later, he was trying to do a residency in radiation oncology, and my good friend, Stanley Order, who was the head of radiation oncology at Johns Hopkins [and a clinical collaborator with Hybritech], called me up and said, 'Howie, there's a guy here that's applying for one of two residencies.' It's a very prestigious position. He said, 'There are lots of applicants and we only take two positions a year. This guy looks really good, but he says he worked in Ivor's lab, but he doesn't list you or Ivor as a reference. Do you know the guy?' I said, 'Stanley, do me a favor will you? Blackball him.' And he did. And I said, 'Try to let him know that it comes from me.' Revenge is always a dish eaten better cold." Majda did his residency at the University of Arizona. He is employed today by Kaiser Permanente in Los Angeles as a radiation oncologist. He declined to be interviewed for this study, so his version of what happened is unavailable.

"There was a backlash. I mean, as it became more and more known within the university that I was doing this, there were people that were very disgruntled or people who were unhappy. You know, they asked, 'How could I possibly do both?'" Faculty members at the School of Medicine and the university proper huddled to determine a course of action, but, as Royston emphasizes, there was little to be done. There were no formal prohibitions to invoke:

> There were some meetings held about me. The university faculty met and discussed how I was able to do all that [start the company and satisfy all academic obligations], and they found out that I hadn't done anything wrong, so there was nothing they could do. I mean, I had disclosed it all to the administration.

The close links between Royston's lab and Hybritech's research and product development operations also drew scrutiny from university administrators, and some suspicion from faculty colleagues. No one at the School of Medicine had ever started a company to capitalize on research conducted in UCSD laboratories. Some faculty members were uncomfortable with the idea, and others were outspokenly opposed to it. And while Royston held a piece of the company and served as a director, he was simultaneously collaborating with the firm as a scientific investigator in his academic laboratory. The lure of profits in this kind of arrangement, some worried, could corrupt the intellectual integrity of the scientific process. From 1980 to 1985, Royston received over $1 million in grants from Hybritech to test the company's monoclonal antibodies in the clinic. As other UCSD bioscientists began following Royston's lead, and, as more money streamed into university laboratories from private industrial sources, concerns about faculty conflicts of interest were voiced on campus with greater frequency and at higher volumes. In 1985, UCSD biochemist Russell

Doolittle publicly expressed serious reservations about the commercialization of scientific knowledge. He believed that the trend was encouraging secrecy and inhibiting communication and cooperation within the local scientific community: "There used to be a good, healthy exchange of ideas and information among researchers at UCSD, the Salk Institute, and Scripps Clinic. Now we are locking our doors. The threat to scholarship is serious indeed."[72]

But the flow of funds from industry to the university's life science laboratories was never retarded. The UC administration was plainly encouraging schools, departments, and faculty members to collaborate with private commercial entities, in order to pick up the slack created by receding government support, and, according to university policy, the mere fact of participation in an industrial project did not constitute a conflict of interest.[73] In 1984, Robert Petersdorf, dean of the UCSD School of Medicine averred: "There have been people with industrial ties and they have been carefully examined. If we had a messy situation, we'd know about it."[74] When asked by a journalist to comment, Royston defended his personal operating methods as legitimate means of advancing the school's institutional mission. The financial gains that he was enjoying from the commercialization of his research, and the professional rewards he was reaping from his collaborations with Hybritech, did not, in his opinion, constitute a threat to the integrity of science, the medical

---

[72] Warren Froelich,"Genetics Out of the Lab: Academia Too Close to Gene Business?" San Diego Union, January 3, 1985. Doolittle's first public statements on the issue came in the midst of a 1980 priority dispute with Scripps scientist Richard Lerner over the invention of a vaccine technology.

[73] UCSD's efforts to strengthen university-industry connections began in earnest after the arrival of Richard Atkinson as chancellor in 1980. See John Markoff, "An Information Revolution Revives Its Economy," New York Times, March 24, 1997.

profession, or the University of California: "The research we are doing has been judged by the university to be a contribution to society, even if there is a benefit to Hybritech and me."[75] Royston became inured to rebuffs and reproofs: "Criticism comes with the turf. Most people don't believe you can serve two masters."[76]

Royston's relations with a number of his colleagues deteriorated. "There were problems," he says, "jealousies, stuff like that." Others have made similar observations. Bill Otterson, late director of UCSD Connect, a university extension office established to promote high-tech entrepreneurship and the commercialization of research conducted at UCSD, saw that, over time, Royston became disaffected in his institutional role. He refused to conform to the traditional academic mold, and his insistence on autonomy was, at times, a source of tension: "Ivor Royston was a model entrepreneur, and as he became more and more entrepreneurial, he fit in less and less with the faculty. A lot of jealousy built up among the faculty, and Ivor didn't do an awful lot to help that." To San Diegans working in the life sciences, Royston's success was conspicuous. Hybritech grew from a tiny start-up in 1978 to a major diagnostics manufacturer with a market capitalization of nearly half a billion dollars in 1985. The sale of the company to Eli Lilly was front page news in the city, and it was well known that individuals and organizations holding substantial stock in Hybritech had realized tremendous gains. Royston was thereafter able to say: "My success is

---

[74] Warren Froelich, "Biotech: Area may be a New Mecca," San Diego Union, January 23, 1984.

[75] Warren Froelich,"Genetics Out of the Lab: Academia Too Close to Gene Business?" San Diego Union, January 3, 1985.

[76] Ann Gibbons, "The Man Who Made Millions by Marketing Monoclonal Antibodies," The Scientist 3, 5, 1989: 1.

beyond my greatest dreams." He had made millions. Royston's family and friends were probably delighted by his good fortune, but, apparently, not all of his professional colleagues were thrilled in the same way. Some, at least, felt vaguely that the gains were ill-gotten.

After Hybritech was sold, Royston began to display some of the trappings of wealth. He started parking a blue Ferrari in his reserved space in the UCSD Cancer Center parking lot – except on those days when he drove his yellow one. He and his wife, Collette, became known around town as civic activists, philanthropists, and patrons of the arts. Their names began to appear regularly in Burl Stiff's society column in the 'Lifestyle' section of the San Diego Union – inches devoted to the comings and goings of the city's most exclusive set. As monoclonal antibody research picked up steam in the scientific community, Royston became one of the top recipients of grant money at the medical school. He achieved notoriety in science, business, and the popular press as a champion of 'magic bullets.' As a success story in both academic research and high-tech industry, as San Diego's dashing cancer warrior, Royston was asked repeatedly by journalists to comment on scientific entrepreneurship and the marvelous promise of monoclonal antibodies in the battle against dread disease. His visibility in the public eye and his avid promotion of hybridoma technology, his companies, and, by extension, himself, did not always sit well with his professional peers.[77]

---

[77] For instance, while Royston tried to generate excitement about the potential of hybridoma technology in medicine, Dr. Robert O. Dillman, his colleague at the UCSD Cancer Center, was at pains to point out that despite all the hype surrounding monoclonal antibodies, they had not yet contributed to any real improvements in cancer treatment. It appeared that they would soon substantially improve the diagnosis of cancer, and, in theory, they suggested new treatment modalities. To cancer patients,

After his involvement with Hybritech had been reviewed and approved by university committees, Royston assumed that his academic career would not be affected by his colleagues' private reactions to his entrepreneurial activities. He carefully followed all of the university's rules governing faculty participation in industry and scrupulously disclosed all required information concerning compensation, equity holdings, and research support, in order to avoid any appearance of impropriety. Eventually, though, he realized that his assumption was mistaken. In 1985, John Mendelsohn, director of the UCSD Cancer Center, and a driving force behind its establishment six years earlier, left to chair the Department of Medicine at the Memorial Sloan Kettering Cancer Center in New York City – one of the few institutions that would count as a step up for him. Royston says that he would have entertained the idea of serving as Mendelsohn's replacement, but that his name was never mentioned in discussions on the topic. The idea of directing a research organization designated by the National Cancer Institute as one of a select group of Comprehensive Cancer Centers held some appeal for him, but he had been assigned – and, to a certain degree, had assigned himself – to a marginal position within it. His perceived waywardness had exacted a cost. "I found," Royston says, "that I was not really taken very seriously at the time because they felt uncomfortable about somebody who was so entrepreneurial, or involved with business. I can see that, you

---

however (apart from a few cases in which experimental therapies had apparently effected poorly understood remissions), monoclonal antibodies had still to deliver benefit one. Dillman tried to deflate what he considered overblown expectations for hybridoma technology in oncology: "The initial enthusiasm for it was more than was warranted. I still think it is something with great promise, but it's not ready for widespread use at all." Quoted in Warren Froelich, "'Magic Bullets' Get Another Shot," San Diego Union, March 3, 1986, p. B1.

know, I had a price to pay there, not being considered." Royston had been involved with the UCSD Cancer Center from the time of its inception, but the directorship went to Dr. Mark R. Green, a lung cancer expert who arrived at UCSD after him in 1979. Royston didn't object to Green's selection, but never forgot what he perceived to be a slight from the faculty. He began to chafe at the notion that he wouldn't be able to exert more influence on the direction of the Cancer Center (and five years later, he would leave the university to strike out on his own, with the founding of the San Diego Regional Cancer Center).[78]

Through 1984, none of Royston's business or scientific activities provoked any official questioning from the university beyond standard reviews of compliance with disclosure rules. Soon after, though, in 1985, Royston had to defend himself against formal allegations of misconduct. He was forced to answer charges that certain of his actions constituted conflicts of interest and commitment. The first trouble erupted at the La Jolla VA Medical Center, when Dr. Robert O. Dillman, the head of the 'hemoc' (hematology and oncology) division of the hospital (and assistant director of the UCSD Cancer Center, and a long-time clinical collaborator with Royston), refused to

[78] In the late 1980s, Royston tried to persuade the university to let him set up his own research unit on campus. He says: "I was getting pretty antsy with the leadership at the university and the Cancer Center and the bureaucracy, and I just wanted to do something on my own. I knew the chancellor [Richard Atkinson] quite well, and I said, 'You know, I like being affiliated with the university, but I'd like to start my own biotechnology research center or something like that' – something like what Gallo has done subsequently now in Baltimore – 'and if the university would throw in the land, we could build it on the university.' I'd met some real estate developers that were interested in getting involved, and I put a whole bunch of proposals together to show the university, but it just didn't go anywhere." After this attempt failed, Royston left, in 1990, to open his own private research institute, now renamed the Sidney Kimmel Cancer Center.

sign Royston's time cards.[79] Dillman asserted that the figures on the sheets did not

[79] From 1982 to 1985, Dillman and Royston published extensively together. They reported results from numerous clinical studies performed cooperatively (see the partial list below). The long stream of co-authored papers ended abruptly after the time card incident. R.O. Dillman, I. Royston, B.L. Meserve, and J.C. Griffiths, "Alteration of peripheral blood lymphocyte populations in plasma disorders," Cancer 48, 1981: 2211-2217; R.O. Dillman, C. Greco, I. Royston, R. Roth, and M.R. Green, "Extracellular paraprotein globules in a patient with monoclonal gammopathy," Archives of Pathology & Laboratory Medicine 106, 1982: 275-277; R.O. Dillman, D.L. Shawler, R.E. Sobol, H. Collins, J. Beauregard, and I. Royston, "Murine monoclonal antibody therapy in two patients with chronic lymphocytic leukemia," Blood 59, 1982: 1026-1045; R.O. Dillman, H.H. Handley, and I. Royston, "Establishment and characterization of an EBV-negative lymphoma B cell line from a patient with diffuse large cell lymphoma," Cancer Research 42, 1982: 1368-1373; R.O. Dillman, R.E. Sobol, H. Collins, J. Beauregard, and I. Royston, "T101 monoclonal antibody therapy, in chronic lymphocytic leukemia," pp. 151-171 in Hybridomas in Cancer Diagnosis and Therapy, eds. M. Mitchell and H. Oettgen, New York: Raven Press, 1982; R.E. Sobol, R.O. Dillman, D. Smith, S. Ferrone, K. Imai, M.C. Glassy, D. Shawler, and I. Royston, "Phase I evaluation of monoclonal anti-melanoma antibody in man," pp. 199-206 in Hybridomas in Cancer Diagnosis and Treatment, eds. M. Mitchell and H. Oetggen, New York: Raven Press, 1982; R.O. Dillman, R.E. Sobol, and I. Royston, "Phase I trials of murine monoclonal antibodies to tumor associated antigens: Preliminary observations," pp. 915-920 in Protides of the Biological Fluids, Proceedings of the 29th Colloquium, ed. H. Peeters, Oxford: Pergamon Press, 1982; I. Royston and R.O. Dillman, "Monoclonal antibody serotherapy of chronic lymphocytic leukemia (CLL)," pp. 621-622 in Advances in Comparative Leukemia Research, eds. D.S. Yohn and J.R. Blakeslee, New York: Elsevier North Holland, 1982; R.O. Dillman, R. Taetle, S. Seagren, I. Royston, J. Koziol, and J. Mendelsohn, "Extensive disease small cell carcinoma of the lung: Trial of non-cross resistant chemotherapy and consolidation radiotherapy," Cancer 49, 1982: 2003-2008; J.A. Young, R.O. Dillman, S.L. Seagren, R. Taetle, R.E. Rentschler, J.W. Lea, T.J. Lehar, M.R. Green, W. Stanton, J. Mendelsohn, and I.R. Royston, "Non-cross resistant chemotherapy and consolidation radiotherapy for small cell carcinoma of the lung," Cancer Treatment Reports 66, 1982: 1399-1401; R.O. Dillman, J.C. Beauregard, J. Mendelsohn. M.R. Green, S.B. Howell, and I. Royston, "Phase I trials of Thymosin Fraction 5 and Thymosin 1," Biological Response Modifiers 1, 1982: 35-41; R.E. Sobol, R.O. Dillman, J.C. Beauregard, A.L. Yu, J.W. Lea, H. Collins, S. Wormsley, M.R. Green, R.R. Ellison, and I. Royston, "Results of early trials using murine monoclonal antibodies as anti-cancer therapy," pp. 417-425 in Protides of the Biological Fluids, Proceedings of the 30th Colloquium, ed. H. Peeters, Oxford: Pergamon Press, 1983; R.O. Dillman, J.C. Beauregard, M.R. Green, J.W. Leu, R.E. Sobol, and I. Royston, "Chronic lymphocytic leukemia and other chronic lymphoid proliferations: Surface marker phenotypes and clinical correlations," Journal of Clinical Oncology 1, 1983: 190-197; R.O. Dillman, J. C. Beauregard, M.I. Zavanelli, B.L. Halliburton, S. Wormsley, and I. Royston, "In vivo immune restoration in advanced cancer patients after administration of Thymosin Fraction Five or Thymosin Alpha One," Journal of Biological Response Modifiers 2, 1983: 139-149; R.O. Dillman and I. Royston, "Using monoclonal antibodies to treat leukemia and lymphoma," Drug Therapy 8, 1983: 62-74; C.A. White, R.O. Dillman, and I. Royston, "Membranous nephropathy associated with an usual phenotype of chronic lymphocytic leukemia," Cancer 52, 1983: 2253-2255; R.E. Sobol, R.O. Dillman, S. Halpern, D.L. Shawler, P. Hagan, S. Ferrone, M.C. Glassy, and I. Royston, "Serotherapy and radioimmunodetection of tumors with monoclonal antibodies," pp. 256-281 in Cellular Oncology; New Approaches in Biology, Diagnosis, and Treatment, eds. P. Moloy and G. Nicolson, New York: Praeger, 1983; J. Mendelsohn, R.O. Dillman, and I. Royston, "Use of biological response modifiers in the management of cancer," pp. 167-193 in Management of Advanced Cancer eds, P. Periman and E.D. Savlol, New York: Masson Publishing, 1983; R.O. Dillman, J.A. Koziol, M. Zavanelli, J.C. Beauregard, B.L. Halliburton, and I. Royston, "Immunocompetence in cancer patients – assessment by in vitro stimulation tests and quantification of lymphocyte subpopulations," Cancer 53, 1984: 1484-1491; R.O. Dillman, J.C. Beauregard, R.E. Sobol, S.E. Halpern, P.S. Hagan, R. Bartholomew, and I. Royston, "Lack of radioimmunodetection and complications associated with monoclonal

accurately reflect the time that Royston was devoting to patient care and his VA assignment. The root of the problem, according to Dr. J. William Hollingsworth, the hospital's chief of medicine, was that Royston was far more dedicated to his research at the UCSD Cancer Center than he was to looking after patients in the VA wards: "He spent all his time getting grants together for the university. This was all well and good, but it became his driving activity."[80] Royston countered: "My perception is that I put in an enormous number of hours at the VA. I put in more – many, many more – hours than the required twenty-five per week."[81]

The matter exploded into a full blown controversy when it came to light that Royston had paid a UCSD medical fellow out of his own pocket to cover his shifts at the VA over an extended period, while he was away attending scientific meetings. Dr. Jacqueline Parthmore, the chief of staff at the VA, had not been informed about the arrangement, but said later: "I don't think it is an acceptable practice. I would be very upset if I was aware that was occurring. I would put a stop to it."[82] An administrative inquiry was conducted. Royston defended his creativity in this way: "This particular fellow is a very good physician. The upshot was the patients got excellent care; I was

---

anticarcinoembryonic antigen antibody cross-reactivity with an antigen on circulating cells, Cancer Research 44, 1984: 2213-2218; R.O. Dillman, D.L. Shawler, J.B. Dillman, and I. Royston, "Therapy of chronic lumphocytic leukemia and cutaneous T-cell lymphoma with T-cell monoclonal antibody T101," Journal of Clinical Oncology 2, 8, 1984: 881-891; D.L. Shawler, M.C. Miceli, S.B. Wormsley, I. Royston, and R.O. Dillman, "Induction of in vitro and in vivo anticancer modulation by the anti human T-cell monoclonal antibody T101," cancer Research 44, 1984: 5921-5927.

[80] Rex Dalton, "Dr. Royston's Ideas Bring Fame, Trouble," San Diego Union, December 7, 1986.

[81] Dalton, "Dr. Royston's Ideas Bring Fame, Trouble."

[82] Dalton, "Dr. Royston's Ideas Bring Fame, Trouble."

able to go to my meetings; and there was no problem."[83] Hollingsworth, however, was evidently not satisfied that all was well. What Royston considered a flexible approach to scheduling, his boss treated as a serious breach of professional ethics. Hollingsworth told reporters that he asked Royston to resign. Royston claims that it was his idea to step aside. As he remembers it, he conceded to Hollingsworth that the VA oncology program needed a physician who would be more involved with patient care. Then, he says, he volunteered his resignation, and suggested that Hollingsworth hire a replacement who could maintain a greater presence in the hospital. In any case, Royston left his clinical assignment at the VA hospital on June 9, 1985, and became a full-time researcher and director of the clinical immunology program at the UCSD Cancer Center. Unfortunately, the incident wasn't quickly forgotten by members of the local cancer research community.

Things got worse for Royston a little over two years later, in September of 1987, after he had sold his stake in Hybritech and had co-founded Idec with Bob Sobol, Ron Levy, Howard Birndorf, and Brook Byers. This time, the problem had to do with Royston's multiple roles as a faculty member and federally funded investigator at the university, and as a consultant, director, and shareholder at Idec. Royston's research projects at UCSD included clinical trials of anti-idiotype monoclonals developed by Hybritech and Idec against B cell lymphomas. He was not being paid by either company for conducting these studies, but he did receive money from both for consulting services, along with free technological assistance, and he

[83] Dalton, "Dr. Royston's Ideas Bring Fame, Trouble."

held a five percent ownership share in Idec while warming a seat on the company's board of directors. Shortly after Royston's association with Idec was brought to the attention of the National Cancer Institute, which was funding work in his UCSD laboratory, a team of three auditors from the National Institutes of Heath division of management survey and review traveled to San Diego from Maryland with questions about how Royston's company business was to be distinguished from his university research. To further complicate matters, when Royston's activities came under federal scrutiny, the university decided that it, too, would take a look at the arrangements that obtained between Royston's lab, the Cancer Center, the medical school, and the Idec Corporation. The inquiries were triggered by an anonymous letter to the NCI that accused Royston of improprieties – misuses of federal funds. To this day, Royston doesn't know who sent the letter, but he's certain that:

> It was somebody within the system, somebody at the university or the VA. I got the letter under the Freedom of Information Act. It was sent to the director of the NCI, Vince De Vita, but they spelled his name wrong, so I know it was not an oncologist, because they wouldn't have gotten the name wrong. But it was somebody in the university system that really had a problem.

Royston's was one of five federal grants at UCSD that simultaneously became subjects of the NIH investigation. His was the largest, by far. Royston was set to receive $870,495 from the NCI to conduct research on anti-cancer monoclonal antibodies. Mark Green, the director of the UCSD Cancer Center, was named as the principal investigator on two additional grants that were audited – a $236,951 'core' grant for the NCI designated Cancer Center, and a $135,482 award from the National Institute of General Medical Sciences for Green's leukemia research. Green, like

Royston, served Idec as a paid consultant. He had received stock in the company as compensation. The other grants also came from the National Institute of General Medical Sciences, and belonged to two UCSD scientists, John F. Hansborough and Steven T. Boyce. Both were associated with a San Diego biotech company called Clonetics Corp., as shareholders and members of the firm's board of directors. The company was cloning human skin cells and selling them to commercial laboratories for use in the testing of drugs, cosmetics, and pesticides. Hansborough was the director of the burn center at the UCSD Medical Center, located in the San Diego's Hillcrest neighborhood. He was receiving $344,328 from the NIH to support an attempt to create 'full-thickness, prosthetic' skin to be used in grafts for burn victims. The government was supplying Boyce's university laboratory with $137,390. Boyce was working on immune suppression in burn victims, in order to facilitate skin transplants. Just as was the case with the grants assigned to Royston and Green, possible conflicts of interest were at issue in the Hansborough and Boyce inquiries.[84]

Royston denied any wrongdoing (as did the other scientists). He told the San Diego Union: "I am not worried. Any allegations are false. I try hard to operate in a conflict-free, above-board manner."[85] He had his laboratory staff review all pertinent records, to ensure that everything was in order. It was discovered that not all patients enrolled in the Idec trials had signed UCSD consent forms. The making of anti-idiotype antibodies against B cell lymphoma required the removal of patients' tumor

---

[84] Rex Dalton, "Probe at UCSD Raises Questions: Federal Auditors Focus on Ties Between Publicly Funded Researchers, Industry," San Diego Union, September 20, 1987, p. B1.

[85] Rex Dalton, "U.S. Probing Five Research Grants to UCSD," San Diego Union, September 16, 1987, p. B1.

cells, so patients had to give their permission. Some of the clinical trials were being conducted for Idec by Ron Levy at Stanford and by others at the University of Washington in Seattle. Patients enrolled at those sites had signed local consent forms. Dr. Katherine Parker, one of Royston's assistants wrote an unsolicited letter to the UCSD Human Subjects Office informing them of the situation. Parker indicated that UCSD forms were being sent to all enrolled patients and that all future participants in the studies would be required to sign UCSD documents. The UCSD Office of Business Affairs was informed about the possible violation of patient's rights, and, after looking into the matter, became uneasy about the university's exposure to financial risk. Business Affairs determined that Idec's product liability insurance was inadequate. They were afraid that in event of a judgment for a plaintiff in a lawsuit seeking reparations for harm caused by an experimental drug, the University of California would take the hit because of its deep pockets. The company and the university renegotiated the insurance terms of their partnership. In addition, while Royston had filed all required paperwork for disclosures of possible conflicts of interest, and his personal involvement with Idec had been approved, the university concluded that intellectual property matters in the collaborative project were poorly defined and needed to be specified in formal contractual agreements. It was not clear how rights to inventions emerging from the collaborative project would be assigned. Negotiations on intellectual property arrangements were initiated in order to protect the economic interests of the UC Regents.

Eventually, the legal questions about the Idec/UCSD interchange were settled to the satisfaction of the university. No one in the administration made any criticism

of the manner in which Royston had been managing the research or his laboratory. The NIH auditors reviewed documentation and financial records, conducted a series of interviews, and then left town. In December, the agency released a report on the findings of its investigation, and NIH spokesman Donald M. Ralbovsky issued a summary statement: "Nothing has been found by the inquiry to support the allegations of improper actions on the part of any of the four investigators."[86] Representatives of the UCSD Office of Academic Affairs and the School of Medicine commented publicly that they were pleased with the results of the inquiry, but not surprised. Royston's response was, in effect, 'I told you so.' He said, "You know, it was always above board. It was investigated and I was exonerated."[87] He acknowledged that it was sometimes difficult for him to balance obligations to UCSD and to Idec, but he argued that his commercial activities contributed to the mission of the university: "I have to admit now with Idec, it is a strain, but it always is with a start-up. I do this out of my own convictions that this is the right thing for me to do, that this is the way to get solutions, and to move things ahead faster to benefit society."[88] To critics voicing concerns about university faculty members starting companies, Royston said: "If you ever get lymphoma, you will be glad I started Idec."[89]

The formation of the biotechnology industry in the late 1970s and the early to mid-1980s depended on social reorganizations as well as scientific accomplishments.

---

[86] Bob Corbett, "UCSD Researchers Cleared in Handling of Federal Grants," San Diego Union, December 11, 1987, p. B3.

[87] Rex Dalton, "U.S. Probe Clears Local Scientists," San Diego Union, December 11, 1987, p. B1.

[88] Dalton, "Dr. Royston's Ideas Bring Fame, Trouble."

As one of the entrepreneurial pioneers in the field, and one of the most visible symbols of change in San Diego, Royston bore the brunt of conservative reactions against the privatization of academic research. Mark Green, Royston's Cancer Center colleague and his 'co-defendant' in the NIH probe, remarked: "It's fair to say that in Ivor's rush to get things done, there are people who feel he didn't stick with the culture of the village. This is not a guy who goes slowly and he's not shy." Royston concurs: "I know other people who have done what I have done but kept a low profile, and therefore, got in less trouble. I was always proud of what I had done and I didn't want to hide behind a rock. Therefore I became an easy target."[90] Dr. Sam Halpern, a professor of radiology at the UCSD School of Medicine, confirms that Royston ruffled feathers by appearing to revel in both his professional achievements and his commercial success:

> There was a lot of jealousy. A lot of jealousy. Ivor's not the first academic who ever made money. I don't begrudge Ivor having become a millionaire. That's no skin off my nose. I don't care. More power to him, you know? He didn't take anything away from that Cancer Center down there. He didn't take anything away from this VA, or from the university. These were petty jealousies. And in this case, I fault the university, not that Ivor was all that easy and reasonable to deal with, because he wasn't. And there were conflicts that occurred between he and the university, flashpoints that didn't have to occur, but Ivor didn't do anything to keep it from happening, and you could see what they were going to be.

In any event, before faculty entrepreneurs like Royston began founding biotech start-ups like Hybritech and Idec, academic life scientists with industry connections were exceptions rather than the rule on the campuses of major research universities in

---

[89] Dalton, "Dr. Royston's Ideas Bring Fame, Trouble."

[90] Ann Gibbons, "The Man Who Made Millions by Marketing Monoclonal Antibodies."

this country. As Royston himself notes: "It's much more acceptable now, and more the norm, for university professors to be involved with their companies. If you're not involved with a company, often, you'll wonder, well, that guy's really not that good, because most people are involved with companies, one way or another, as a consultant or as a founder, whatever." Academic culture has been transformed. The prevailing attitude is that current institutional means of ensuring the integrity of research and education in academic settings are generally sufficient. From this point of view, Royston's administrative trials and tribulations can be interpreted as early tests of the system's capacities to provide adequate oversight. Inquiries into Royston's activities at UCSD set precedents. For most faculty members, the issues were decided with finality. Sam Halpern's view of existing institutional mechanisms and policy frameworks – which were shaped in part by interpretations of Ivor Royston's entrepreneurial pursuits, industrial ties, and laboratory management decisions – is now a typical one:

> I sit on committees, oversight committees, what we call conflict of interest committees, and I always give a good, hard look because, by definition, there is a conflict of interest if a scientist working with a corporation and they're a university employee. The university has a mission – education, public welfare, that sort of stuff. Anytime somebody is allied with a corporation, doing the research for the corporation, you have to say, 'OK, we're going to have an oversight committee,' and, 'OK, we're going to call this a conflict of interest with oversight. And if there's intellectually honest oversight, and you see that this supports the university's mission, I have no problem with it. I do this myself, you know? I worked for Hybritech for many years. I had tremendous sums of money coming in. One year, between private and public money, I must have had half a million dollars coming in. I was grinding out research like mad. But it has to be watched.

Halpern was a collaborator with Hybritech for several years in the early 1980s in extensive clinical trials of radiolabeled monoclonal antibodies in diagnostic imaging applications.[91] He took money from the company for research and in exchange for consulting services, but he never accepted stock that he was offered, in order to avoid feeling beholden. "I've been able to make an accommodation," he has said, "without violating my principles. I don't own any stock in the company and as a consequence I

---

[91] See P. Stern, S. Halpern, P. Hagan, G. David, and W. Desmond, "Comparison of an I^{125} labeled monoclonal anti-tumor antibody with Ga^{67} in a nude mose-human colon tumor model," Clinical Nuclear Medicine 5 (suppl.), 1980: S19; S.E. Halpern, P.H. Stern, P.L. Hagan, A.W.N. Chen, G.S. David, W.J. Desmond, T.H. Adams, R.M. Bartholomew, J.M. Frincke, and C.E. Brautigan, "Radiolabeling of monoclonal anti-tumor antibodies, comparison of I^{125} and In^{111} anti-CEA with Ga^{67} in a nude mouse-human colon tumor model," Clinical Nuclear Medicine 6, 1981: 453; P. Stern, P. Hagan, S. Halpern, A. Chen, G. David, T. Adams, W. Desmond, K. Brautigan, and I. Royston, "The effect of the radiolabel on the kinetics of the monoclonal anti-CEA in a nude mouse-human colon tumor model," pp. 245-253 in Hybridomas in Cancer Diagnosis and Treatment, New York: Raven Press, 1982; S.E. Halpern, P.L. Hagan, P.R. Garver, J.A. Kozol, A.W.N. Chen, J.M. Frincke, R.M. Bartholomew, G.S. David, and T.H. Adams, "Stability, characterization, and kinetics of I^{111} labeled monoclonal anti-tumor models," Cancer Research 43, 1983: 5347-5355; P.L. Hagan, S.E. Halpern, A.W.N. Chen, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "Comparison of In^{111} Fab and whole In^{111} in anti-CEA monoclonal antibody (MoAb) in normal mouse and human colon tumor models," Journal of Nuclear Medicine 24, 1983: 77; S.E. Halpern, R.O. Dillman, P.L. Hagan, J.D. Dillman, I. Royston, R.E. Sobol, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "The clinical evaluation of In^{111} labeled monoclonal anti-melanoma antibodies for human scanning," Journal of Nuclear Medicine 24, 1983: 15; S.E. Halpern, P.H. Stern, P.L. Hagan, A.W.N. Chen, R.M. Bartholomew, J.M. Frincke, G.S. David, and T.H. Adams, "The labeling of monoclonal antibodies with In^{111}. Technique and advantages compared to radioiodine labeling," in Radioimaging and Radioimmunotherapy, eds., S. Burchiel and B. Rhodes, New York: Elsevier North Holland Biomedical Press, 1983; R.O. Dillman, K.F. Witztum, J.B. Dillman, P.L. Hagan, M. Clutter, J.M. Frincke, R.M. Bartholomew, G.S. David, D.J. Carlo, and S.E. Halpern, "Immunoscintigraphy with $indium^{111}$ conjugated monoclonal antibodies," in Protides of the Biological Fluids, Vol.32, , ed. H. Peeters, Oxford: Pergamon Press, 1985; S.E. Halpern, R.O. Dillman, K.M. Witztum, J.F. Shega, P.L. Hagan, W.M. Burrows, J.B. Dillman, M.L. Clutter, R.E. Sobol, J.M. Frincke, R.M. Bartholomew, G.S. David, and D.J. Carlo, "Radioimmunodetection of melanoma utilizing In^{111} 96.5 monoclonal antibody – a preliminary report," Radiology 155, 1985: 493-499; P.L. Hagan, S.E. Halpern, A. Chen, L. Krishnan, J. Frincke, R.M. Bartholomew, G.S. David, and D. Carlo, "In vivo kinetics of radiolabeled monoclonal anti-CEA antibodies in animal models," Journal of Nuclear Medicine 26, 1985: 1418-1423; J.M. Frincke, C.H. Chang, C.N. Ahlem, G.S. David, R.M. Bartholomew, L.D. Anderson, P.L. Hagan, S.E. Halpern, and D.J. Carlo, "Pharmacokinetics of bifunctional antibody delivered In^{111} benzyl EDTA to colon tumors in nude mice," Journal of Nuclear Medicine 27, 1986: 1042; P.L. Hagan, S.E. Halpern, R.O. Dillman, D.L. Shawler, D.E. Johnson, A. Chen, L. Krishnan, J. Frincke, R.M. Bartholomew, G.S. David, and D. Carlo, "Tumor size: Effect of monoclonal antibody uptake in tumor models," Journal of Nuclear Medicine 27, 1986: 422-427; S.E. Halpern, P.L. Hagan, A. Chen, C.R. Birdwell, R.M. Bartholomew, K.G. Burnett, G.S. David, K. Poggenburg, B. Merchant, and D.J. Carlo, "Distribution of radiolabeled human and mouse monoclonal IgM antibodies in murine models," Journal of Nuclear Medicine 29, 1988: 1688-1696.

feel I can do anything I want."[92] Yet, he doesn't criticize those who have taken equity positions and he doesn't consider such arrangements to be unmanageable. This has become the majority opinion among university faculty.[93] Of course, a dissenting minority remains. Russell Doolittle, for example, first spoke out against faculty ties with industry in the 1980. Doolittle is an accomplished scientist, a member of the National Academy of Sciences, and much in demand as an expert on the molecular biochemistry of blood proteins, but he has refused on principle to accept equity holdings in companies, to consult or serve on scientific advisory boards of private firms, or to become involved in any capacity with commercial entities. He has held out steadfastly against the rising tide of commercialization on the UCSD campus for nearly twenty-five years. Doolittle has not changed his mind about conflicts of interest, or conflicts of commitment. In 2003, he said: "I believe universities have sold their souls. There's a neglect of duty when faculty pay so much attention to their companies, rather than their undergraduate teaching."[94] But Doolittle, by his own account, doesn't have much company in his own department, school, and institution.

Decisions regarding the leadership of the UCSD Cancer Center can be used as a barometer of changing attitudes among academic biomedical researchers. In 1985, Ivor Royston was effectively excluded from serious consideration for promotion to the top position in the organization because of his industry connections. Less than twenty

---

[92] Warren Froelich,"Genetics Out of the Lab: Academia Too Close to Gene Business?"

[93] Yong S. Lee, "'Technology Transfer' and the Research University: A Search for the Boundaries of University-Industry Collaboration," Research Policy 1996, 25: 843-863; and Dianne Rahm, "Academic Perceptions of University-Firm Technology Transfer," Policy Studies Journal, 1994, 22: 267-278.

years later, in October 2003, San Diego researcher Dennis Carson was named the new director of the Center. One of Carson's stated priorities for the institution is the development of closer and more extensive ties between faculty researchers and biotechnology companies, in San Diego and elsewhere, in order to speed the translation of the university's basic life science discoveries into new treatments for cancer.[95] Carson is a firm believer in the value of small biotech firms. "Big Pharma," he says, "won't take the risk to do something at an early stage, so biotechs serve as a transition between the academic lab and Big Pharma. They do second stage, and they do sub-licensing. That's what's going on. So, biotech is really important for the universities." Carson has himself been involved in the formation of four biotech companies, Vical, Inc., Triangle Pharmaceuticals, Dynavax Technologies, and Salmedix, Inc.[96] He remains, while directing the UCSD Cancer Center, actively involved in Dynavax and Salmedix, as a board member as well as a shareholder. Like most of his colleagues, he now takes for granted the propriety of faculty involvement in commerce, and he has few reservations about researchers capitalizing on technologies developed at the university. Carson certainly would agree with sentiments that Royston expressed on numerous occasions in the 1980s: "We live in a

---

[94] Eleanor Yang, "Some See Conflict in Transfer of Research to Private Sector," San Diego Union Tribune, October 26, 2003.

[95] Sarah Z. Sleeper, "UCSD's Quiet New Cancer Czar," San Diego Metropolitan, November 2003.

[96] Former Hybritech personnel have been connected to each of the four. Vical, Inc. was seeded originally by Biovest Partners – Hybritech's Ted Greene and Tim Wollaeger. Triangle Pharmaceuticals and Dynavax Technologies both received start-up funding from Forward Ventures, Ivor Royston's risk capital firm, and Dynavax's first office and lab spaces were located at Royston's research institute, the Sidney Kimmel Cancer Center. The present CEO of Salmedix is David Kabakoff, formerly Hybritech's director of in vitro product development.

capitalistic society. Why, because we're academics, should we deprive ourselves of the financial rewards that come with our work? Just because you're an academic you shouldn't have to shut yourself off from one of the basic tenets this country was built on."[97]

UNIVERSITIES, BIOTECH COMPANIES, AND ASYLUMS

What is the character, then, of the scientist's commitment to truth, and to social institutions putatively dedicated to uncovering it? How are relationships between these commitments and the organized accumulation of useful or otherwise valued knowledge to be understood? Should scientific institutions demand exclusive commitments from individual members? Unlike Merton, who considered distinctions between social roles and the persons who perform them relatively unimportant in terms of understanding processes of social organization, sociologist Erving Goffman has maintained that "one cannot think clearly about the claims of commitment or attachment that a social entity makes on its participants without thinking of the limits felt proper on these claims."[98] The concrete realities of organizational life, Goffman reminds his audience, can never be reduced to the efficient coordination of labor power for the achievement of formal organizational purposes. On this view,

---

[97] Ann Gibbons, "The Man Who Made Millions by Marketing Monoclonal Antibodies," The Scientist 3, 5, 1989: 1.

[98] Erving Goffman, Asylums: Essays on the Social Situation of Mental Patients and Other Inmates, New York: Anchor Books, 1961, p. 173. Moreover, as Goffman describes in this book, even in the most coercive of social institutions, such as asylums and prisons, where surveillance and discipline are most oppressive, where daily routines are most closely monitored and regulated, individuals find ways of circumventing administrative control. They find ways of "making out" and "working the system." Persons in these settings seek out or create "free spaces" in which they are able to preserve or construct self-conceptions apart from their institutionally defined roles, and in which they can express their individuality. These spaces and activities comprise what Goffman calls the "underlife" of an institution. And every institution, Goffman suggests, sustains one. See pp. 171-320.

organizations of all kinds (and, it might be added, especially those, like the sciences, that depend on the voluntary commitment of marketable talents and skills) must enlist the cooperation of individuals who can, on most occasions, in accord with the generalized mores of Western culture, rightly expect to be treated, not simply as resources, but as persons.

Members of modern social establishments may internalize institutional or organizational values and ideals to greater or lesser degrees, but they are not required or expected to define themselves wholly in terms of their institutional or organizational affiliations. An individual fully self-identified with the functional, instrumental aspects of an organizational role would be a bizarre sort of one-dimensional person, and, no doubt, an unmitigated disaster for the institution. Social institutions and organizations can hardly demand or encourage this kind of personal loyalty.[99] "Built right into the social arrangements of an organization," Goffman notes, "is a thoroughly embracing conception of the member – and not merely a conception of him qua member, but behind this a conception of him qua human being."[100] Goffman is pointing here to abounding discrepancies between the instrumental ends of social organizations and the personal interests of those who serve them. Of course, individuals situated within social organizations at all levels are, for

---

[99] For an extended treatise on the maintenance of "role distance" as a ubiquitous feature of social life, see Erving Goffman, The Presentation of Self in Everyday Life, New York: Anchor Books, 1959. See, also, Howard S. Becker, "Notes on the Concept of Commitment," American Journal of Sociology, 1960, 66: 32-40; Howard S. Becker and James W. Carper, "Adjustments to Conflicting Expectations in the Development of Identification with an Occupation," Social Forces, 1957, 36: 51-56.

[100] Goffman, Asylums, p. 180.

the most part, acutely aware of these endemic conflicts. Goffman suggests that sociologists ought to be as well:

> The simplest sociological view of the individual and his self is that he is to himself what his place in an organization defines him to be. When pressed, a sociologist modifies this model by granting certain complications: the self may be not yet formed or may exhibit conflicting dedications. Perhaps we should further complicate the construct by elevating these qualifications to a central place, initially defining the individual, for sociological purposes, as a stance-taking entity, a something that takes up a position somewhere between identification with an organization and opposition to it, and is ready at the slightest pressure to regain its balance by shifting its involvement in either direction.[101]

Goffman argues that adequate representations of the internal workings of social organizations must include accounts of the ways in which tensions induced by the ambivalence of persons to the burdens of duty are managed in concrete organizational practice. It is no simple matter, Goffman suggests, to identify 'normative structures' because the actual (as opposed to the ideal) values that a social organization embodies are rooted in the particularized practices that constitute the organization, including the allowances that the organization makes, routinely or exceptionally, for the personal interests and needs of its members.[102] These

---

[101] Goffman, Asylums, pp. 319-320. Goffman's criticism here is directed at Parsonian structural-functionalism. The Parsonian view of the world has fallen out of favor in sociological analysis, but what Goffman termed the "underlife" of institutions remains relatively neglected in the sociological study of organizations. For a recent statement on the centrality of the 'relational self' within formal organizational structures, i.e., a person living an 'underlife' with others, see Carol A. Heimer, "Doing Your Job And Helping Your Friends: Universalistic Norms about Obligations to Particular Others in Networks," pp. 143-164 in Networks and Organizations: Structure, Form, and Action, eds. Nitin Nohria and Robert G. Eccles, Boston: Harvard Business School Press, 1992.

[102] Similar analytical views on organizational life formulated by contemporaries of Goffman include Egon Bittner, "The Concept of Organization," Social Research, 1965, 32: 239-255; David Silverman, The Theory of Organizations, London: Heinemann, 1970; and Karl E. Weick, The Social Psychology of Organizing, Reading, MA: Addison-Wesley, 1969.

accommodations are always negotiable, susceptible to challenge and change by "the slightest pressure." They are also commonly arranged informally, dispensed on an ad hoc basis, unsanctioned by (and sometimes contrary to) officially stated polices. Social scientists regularly describe formal organizations as governed chiefly by the application of universalistic principles, but, as Goffman insists, beneath formal structures will always be found a world regulated by particularized judgments and actions. Consequently, social organizations are obliged to tolerate conditions of normative uncertainty as enduring facts of life. Members are given spaces in which to breath and be human, and provided opportunities for self-expression – and by necessity, for alternatives would entail expanding demands for personal commitment, intrusions on the uncodified bargains that sustain all collective enterprises.

The understanding of organizational life that Goffman presents is pertinent to debates concerning the participation of academic scientists in the commercialization of basic research. The deference that organizations are obliged to show for the personal autonomy of their members is often expressed, as Goffman notes, in the distribution of "rewards or side payments that frankly appeal to the individual in his capacity as someone whose ultimate interests are not those of the organization."[103] It is no different in the sciences. The sciences are today organized as professional disciplines firmly ensconced in privileged institutions. The formalization and institutional success of modern science have profoundly shaped the conditions of contemporary

[103] Goffman, Asylums, p. 178.

scientific work, and also, importantly, what it can mean to people to do this work.[104] Science is today an occupation, not an avocation, as it was once upon a time. Scientific disciplines are today social spaces in which individuals are able to fashion respectable careers. On occasion, fame, fortune, and modest measures of power and influence are available to the few who play the game especially well, or to those lucky enough to find themselves in the right place at the right time. Opportunities for reaping these kinds of rewards are incentives that the profession, in all likelihood, could not do without.

Scientists are, of course, persons with associations and commitments that extend beyond their formal professional duties. They have families, friends, and acquaintances. They have personal preferences, interests, and ambitions. In exchange for the responsible discharge of disciplinary tasks, scientific institutions must make suitable accommodations for these persons and their circumstances. This, no less than technical work conducted at the lab bench, or any other aspect of the profession, is what scientific institutions are about. Professional science has never been solely a quest for truth. If knowing the truth were the only reward to be earned in science, it is unlikely that the profession would have advanced as far and as quickly as it has. But commitments to professional duty are peculiar. As the sciences have become what they are in modern society, it has simultaneously become necessary for individuals engaged in scientific work to distance themselves, to some degree, from their formal

---

[104] The classic statement on professionalized science as a personal calling is, of course, Max Weber's "Science as a Vocation," pp. 129-156 in From Max Weber: Essays in Sociology, eds. H.H. Gerth and C. Wright Mills, New York: Oxford University Press, 1946. But Weber arguably described unbalanced persons.

professional roles.[105] And, what is more, it is incumbent upon scientific institutions to allow them the freedom to do so.

As Goffman points out, the emoluments that organizations offer to personnel often include "rewards that the recipient can carry off the premises and use at his own discretion without implicating other members of the organization."[106] In the life sciences, the freedom to capitalize on one's own research can be called a "side payment" to those who have, in fact, fulfilled their duties and advanced knowledge and technical capacities in the fields of biology, chemistry, and other specialties. That this has become controversial is no great surprise. Prerogatives of individuals and private concerns to profit from research financed by public monies can certainly be questioned. But the formulation of rules governing such activities – and, indeed, the very recognition of 'unregulated' arrangements to which rules might be applied – has followed the entrepreneurial creation and exploration of new scientific and economic spaces. The informal, mostly unspoken codes of conduct that do, in fact, order activities in these spaces, have been, like those in any other sphere of action,

---

[105] This doesn't mean that scientists can't throw themselves into their work, but it hardly makes sense to separate one's identity from an avocation in this way. The imposition of professional discipline in the sciences has made it difficult for individuals to pursue 'science as a vacation.' At the same time, it has provided opportunities for pursuing 'science as a racket' (here, I do not mean to imply misconduct or departures from 'good science'). Probably, in rare instances, there are persons who are able consistently to answer 'a calling' to one or the other extreme. For most, however, doing science surely consists in a balancing act, the reconciliation of personal commitments with what are often described as (but which can seldom be honored as) impersonal professional obligations. Dedications that customarily precede certain kinds of scientific publications (books, mainly) regularly allude to such contradictions. They often include expressions of perceived conflict between private and professional identities. In them, debts are acknowledged, not only to helpful colleagues, but to friends and family, sometimes in ways that echo Weber's ruminations on the meaninglessness of purely instrumental rationales for action. This inscription from a scientific work is an example: "To Nip, Danny, and Chris, without whom little matters and virtually nothing is much fun."

[106] Goffman, Asylums, p. 179.

established in actual practice, and not unambiguously. They have been drawn from the worlds of science and business, and the broader common culture, and, within them, there is everywhere room for maneuvering and the striking of bargains regarding how to proceed with business at hand, not to mention room for negotiating what that business will be.

Obviously, idealizing principles deemed to reflect genuine scientific values can be applied post hoc and found to conflict with evolving conventions in biotechnology, where the worlds of science and business merge. But the same procedures could be employed to evaluate traditional arrangements in academic institutions, and they would yield, just as surely, the same results.[107] It is not at all unusual for organizational "side payments" to be dispensed in ways that are extraneous to, or even at odds with, an organization's official mission. That is the whole point of such payments. Goffman gives the following example to illustrate how solutions to problems of organizational commitment are often implemented flexibly, leaving questions of principle hazy and undefined. The determination of actual organizational policies and values is often left to the discretion of individual members who may find it counterproductive to specify just what constitutes appropriate identification with or indifference to an organization's formal ends:

> The managers of a commercial office may be clear about feeling it permissible for clerks and secretaries to select one another for personal relationships – provided that not too much working time is wasted in

[107] Contradictions between official ends and actual practices can be found in any formal organization or institution, for that matter. And in discussions about the propriety of university-industry relations, private firms are often characterized as organizations directed exclusively toward securing competitive advantages and maximizing profits. On the basis of this abstract generalization, many assumptions can be made about the ways in which firms manage knowledge and people, but they may be overdrawn and misleading.

> this way – and just as clearly disapprove of trainees who stay only long enough to check through the courting possibilities before going on to a fresh office and a new pasture. But management may be much more vague as to where between these two extremes the line is to be drawn separating the legitimate incidental use of an establishment as a convenience from illegitimately making a convenience of the institution.[108]

Drawing the line between what is proper and improper regarding the private appropriation of basic research by entrepreneurial life scientists is a problem of the same sort. Academic policies that designate limits to individual conflicts of interest and commitment are not properly understood as mechanisms that insulate academic values from defilement by extrinsic influences. Exactly the opposite is true: they tacitly acknowledge that such tensions are constitutive, ineliminable features of academic institutions, just as they are in any other social institution. They are not simply rules that prescribe behavior. They are, simultaneously, admissions of practical limits to administrative control, prudent endorsements of "free spaces" carved out by individuals exercising their rights to be treated as persons, and not mere instruments of science. Attempts to stipulate fully the range of proper ends to which the products of scientific work can be applied will inevitably test the functional capacities of scientific institutions to exact personal commitments from their members. Conflicts of interest are necessarily countenanced if individuals' voluntary contributions to institutional ends are to be effectively secured.

This fact of modern organizational life complicates efforts to align the ends of academic institutions and the interests of the public in the production and application of knowledge. It problematizes, not only the strict formulation of rules for individual

---

[108] Goffman, Asylums, pp. 192-193.

conduct, but also, concomitantly, any notions of scientific 'purity.' Further, it confounds efforts to define precisely the social roles and obligations of universities and academic research institutions. In the case of biotechnology, the making of technological innovations has been accomplished through the making of organizational innovations, the transfer of scientific knowledge and skills from universities to the marketplace via the creation of unprecedented social arrangements. The growth of commercial biotechnology has emerged, in part, from the pragmatic exploitation by scientists of openings for (bureaucratically) unconstrained action that exist within and extend across formal institutional jurisdictions. This phenomenon indicates the permeability of established boundaries between science and commerce, but not disorder, as some would have it. If Goffman has modern organizations right, and if the sociology of scientific knowledge is analytically sound, then the normative dimensions of life science entrepreneurship can be adequately understood only by taking account of the ways in which the rules that govern it have been created and implemented by participants operating on the ground.

When brought to bear on current problems of university policy, this view complicates efforts to align the ends of science and the interests of industry or the public in the production and application of knowledge. By problematizing notions of scientific purity and the strict definition and enforcement of rules governing the conduct of individual scientists, it concomitantly undermines attempts to define precisely the social roles and obligations of universities and academic research institutions. Drawing hard and fast lines between what is proper and improper

regarding the appropriation of basic research by entrepreneurial life scientists and by private ventures formally linked to the academy is an impossible task.

Practical understandings of this circumstance are not, of course, absent from policy debates. Academic institutions are presently searching for ways to juggle social obligations that may, in practice and in particular cases, generate conflicts of interest and commitment. They are seeking to preserve their traditional missions of education and basic research, while at the same time working to transfer knowledge to the marketplace in order to spur economic growth. Of organizational dilemmas issuing from attempts to discharge these responsibilties simultaneously and from internal disagreements regarding what it might mean to do so, José E. Trías, general counsel for the Howard Hughes Medical Institute, states: "these conflicts are inherent to our research system. There is no practical way to avoid them nor is there only one way to resolve them. The best that universities and other research institutions can aspire to is, as [American jurist] Learned Hand said, 'a tolerable accommodation.' No royal road exists to attain those accommodations concretely."[109]

Many in universities and the life sciences hold to similar views. They hope to fashion acceptable compromises and to steer a middle passage that avoids both an injudicious corporatization of biological research, on the one hand, and the rigid maintenance of institutional and disciplinary boundaries that may inhibit useful scientific contributions to the public welfare, on the other. They are concerned with

---

[109] José E. Trías, "Conflicts of Interest in Basic Biomedical Research," pp. 152-160 in Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century, eds. Frederick B. Rudolph and Larry V. McIntire, Washington, D.C.: Joseph Henry Press, 1996, p. 152. Trías refers here to Judge Hand's definition of justice: "the tolerable accommodation of the conflicting interests of society."

striking a balance that will simultaneously optimize the growth of scientific knowledge in universities and rates of technological innovation in industry. Arthur Kornberg, for example, a Nobel Prize winning chemist, and himself a successful scientific entrepreneur, contends that if entrepreneurial biotech ventures can deliver practical benefits it is because they operate more or less freely in the interstices between academic, corporate, and government bureaucracies. Without underestimating the tensions that may exist between the means and ends of academic knowledge-making and industrial profit-making, or the logistic and technical difficulties involved in commercializing basic research, Kornberg maintains that the goods these firms produce will be enjoyed only so long as this autonomy is preserved. He sees biotech ventures as valuable links between universities and the pharmaceutical trade, as enterprises that may facilitate the speedy transfer of discoveries and drugs from the laboratory to medical practitioners and their patients, as settings in which the objectives of 'basic' and 'applied' research can be balanced and combined in ways that benefit the common good. Consequently, he considers the vitality of entrepreneurial science as something well worth encouraging: "The health and wealth of society," he says, "depend on it."[110]

At the same time, however, Kornberg insists on the necessity of preserving and supporting science as conducted in universities. He worries that "the publicized vigor and successes of biotech companies may foster illusions that basic research can be left

[110] Arthur Kornberg, The Golden Helix: Inside Biotech Ventures, Sausalito, CA: University Science Books, 1995.

to industry."[111] According to Kornberg, the capacity of the pharmaceutical industry to develop new drugs in the future will be impacted most, not by work conducted on its own premises, but by the broadening of bodies of knowledge concerning fundamental chemical and biological processes – in other words, 'basic' science as pursued in academic settings. He believes that focusing work in the life sciences on treatments for specific diseases will not, in the long run, produce the best results for science, for industry, or for physicians and their patients: "Counterintuitive though it may seem to the layman (and, perhaps, even to the scientist), the most cost-effective advances in medicine are not likely to be made by frontal assaults on targeted diseases."[112] The freedom of inquiry enjoyed by academic researchers and flows of public monies to their laboratories are essential, Kornberg argues, because "discoveries are so commonly serendipitous." On this view, as far as scientific progress is concerned, "the best plan would seem to be no plan."[113] Kornberg believes that for all of the bureaucratic trappings of academic disciplines and institutions, and for all of the flexibility built into commercial biotech operations, scientific inquiry in university settings is organized in ways that allow it to take better advantage of unexpected findings and the willingness of individual investigators to pursue risky projects on the basis of judgments unencumbered by calculations of market potential. He advises

---

[111] Kornberg, The Golden Helix, p. 248.

[112] Kornberg, The Golden Helix, p. 10. "As a game," says Kornberg, "medical research resembles pool more than billiards: points are scored no matter which pocket the ball goes into, because each increment in technique and insight can benefit the efforts of researchers on many different diseases."

[113] Kornberg, The Golden Helix., p. 11.

universities to move with caution as they extend their interactions with business and their efforts to commercialize basic scientific research.

Kornberg's view does not suppose any special 'purity' of scientific practice.[114] It is not premised on the notion that science is necessarily tarnished when directed toward commercial ends. It is founded instead on practical knowledge concerning the ways in which organizations sponsoring scientific work function concretely. If this project has contributed to understandings of expanding university-industry relations and the deepening involvement of individual life scientists in commerce it has been by retrieving this kind of organizational knowledge from participants, and by examining, from an historical perspective, how the phenomenon of life science entrepreneurship, and the controversial social transformations to which it has give rise, emerged spontaneously from within academic institutions. To the extent that it has reported on actions and events significant to the evolution of university-industry relations, this study can be described as an historical investigation of "free spaces" created by the normative indeterminacies of organizational life in academic settings, and of

[114] Echoing Merton, Kornberg contends that the scientific enterprise is distinguished by "rather strict boundaries for behavior that are effective in all but the very rare instances of irrationality and criminality," and disciplinary practices that demand "exact and objective descriptions of progress, evidence that can be verified or denied by others." Yet, he invokes no special epistemological privilege for scientific knowledge. The technical discipline to which he refers might be understood simply as a tradition of meticulousness. Science, says Kornberg, "enables ordinary people...to go about doing ordinary things which, when assembled, reveal the extraordinary intricacies and awesome beauties of nature." Further, he appears to be willing to extend the ordinary appreciation of beauty well beyond what philosophers call 'contexts of discovery' to 'contexts of justification' when he remarks: "Can research now be engineered and pursued by formula? Not yet. The technical tools are indispensable, but science remains essentially an art form...[its] probings are determined by emotions, moods, and cultural heritage, much as these also influence the artist." In any event, Kornberg does not suggest that the privatization of science necessarily threatens the integrity of its standards of evaluation. See Kornberg, The Golden Helix., p. 16.

entrepreneurial explorations in San Diego of new technical and organizational possibilities located within them.

BIOTECHNOLOGY'S ETHICAL AND POLITICAL DILEMMAS

In the life sciences and the higher circles of academic politics, debates on the application of biotechnologies are generally concerned with the health and integrity of the scientific enterprise, the goose that lays the golden eggs. In the humanities and social sciences, however, biotechnologies have provoked different sorts of worries in addition. Many in these precincts are trying to decide whether to trust or be wary of the goose itself. Some, as noted above, question whether the privatization of biotechnologies will guarantee fair returns to the public for its contributions to basic science. Others express further concerns, and wonder whether public interests ought to be conflated with the intent of federal policies designed to transfer scientific goods to the marketplace, and whether economic and medical benefits issuing from this development will be distributed equitably.

They also voice reservations and objections having to do with possible environmental hazards associated with uses of genetic engineering, and moral, ethical, and legal dilemmas posed by knowledge of the human genome, uncertainties regarding the status of biological materials and genetic information as private and public properties, and applications of new reproductive technologies.[115] Often these

---

[115] Expressing various opinions on these problems and how they ought to be managed are Elaine Draper, Risky Business: Genetic Testing and Exclusionary Practices in the Workplace, Cambridge: Cambridge University Press, 1991; Daniel J. Kevles, In the Name of Eugenics: Genetics and the Uses of Human Heredity, New York: Knopf, 1985; Daniel J. Kevles and Leroy Hood, eds., The Code of Codes" Scientific and Social Issues in the Human Genome Project, Cambridge, MA: Harvard University Press, 1992; Philip Kitcher, The Lives to Come: The Genetic Revolution and Human Possibilities, New York: Simon & Schuster, 1996; Dorothy Nelkin and Laurence Tancredi, Dangerous

concerns are linked with problems regarding the participation of informed, democratically empowered publics in technological decision-making, public access to and understanding of scientific and technological information, and the social gulf that separates scientific experts and lay constituencies. Many believe that public debates on biotechnology have been shaped by the interests of technocratic elites, and that economic considerations consequently dominate policy-making agendas, crowding out the discussion of social problems associated with biotechnological development.[116]

L. Christopher Plein asserts that prior to 1980, "biotechnology conjured up images of environmental risk and social uncertainty. Today, biotechnology is largely characterized by economic themes such as patent rights, international trade, research funding, and regulatory policy."[117] Plein argues that images of biotechnology in public discourses have been significantly influenced by "the efforts of a well-organized coalition [of scientists and industrialists] to define biotechnology in positive terms."[118] If public opinion polls are any indication,[119] the citizens of developed

---

Diagnostics: The Social Power of Biological Information, Chicago: University of Chicago Press, 1994; Jeremy Rifkin, The Biotech Century: Harnessing the Gene and Remaking the World, New York: Jeremy P. Tarcher/Putnam, 1998.

[116] See Stephen Hilgartner, "The Dominant View of Popularization: Conceptual Problems, Political Uses," Social Studies of Science, 1990, 20: 519-539; Les Levidow, "Biotechnology Regulation as Symbolic Normalization," Technology Analysis and Strategic Management, 1994, 6, 3: 273-288; Christopher L. Plein, "Popularizing Biotechnology: The Influence of Issue Definition," Science, Technology & Human Values, 1991, 16, 4: 474-490.

[117] Christopher L. Plein, "Popularizing Biotechnology: The Influence of Issue Definition," Science, Technology & Human Values, 1991, 16, 4: 474-490; quote on p. 475. See also Christopher L. Plein, "Biotechnology: The Evolution of a Policy Issue," pp. 147-166 in Biotechnology: Assessing Social Impacts and Policy Implications, ed. David J. Webber, Westport, CT: Greenwood, 1990. Cf. Susanna Hornig Priest, "Information Equity, Public Understanding of Science, and the Biotechnology Debate," Journal of Communication, 1995, 45, 1: 39-54.

[118] Christopher L. Plein, "Popularizing Biotechnology," p. 475. See also Sheldon Krimsky, Biotechnics and Society: The Rise of Industrial Genetics, New York: Praeger, 1991.

nations are, in fact, ambivalent about biotechnological progress, well aware that their perceptions of risk are based on insufficient knowledge, and not entirely trusting of the information that they receive from scientists, industry, and governments.[120] They are apparently hopeful that material improvements will follow from bioresearch and industrial development, but uneasy about possible dangers, and divided over the moral implications of manipulating life for commercial (and other) purposes.[121] It seems that many are not yet comfortable with practices like human cloning, research employing human embryonic stem cells, xenotransplantation, the artificial manufacture of human organs, the cultivation of transgenic species, and the like.[122]

In the workaday world of bioscientific practice, these sorts of issues were, for the most part, settled long ago – at least insofar as they concerned the application of

---

[119] For a discussion of flaws in attempts to assess public opinion on biotechnology, see Aidan Davidson, Ian Barns, and Renato Schibeci, "Problematic Publics: A Critical Review of Surveys of Public Attitudes to Biotechnology," Science, Technology & Human Values, 1997, 22, 3: 317-348. The authors argue that representations of public opinions in survey research are constructed or manufactured in ways that incorporate systematic biases.

[120] Andy Coghlan, "Gene Industry Fails to Win Hearts and Minds," New Scientist, 19 June 1993, 138: 4.

[121] Surveys indicate that publics generally consider the use of biotechnologies in medical applications more acceptable than in food and agriculture, and that they deem the genetic manipulation of plants and microorganisms less objectionable than experimentation with animals. On the whole, it appears that respondents in the U.S. are more likely to approve of biotechnological development than Europeans, and that favorable impressions are positively correlated with increased knowledge and understanding of the biosciences. See John Durant, ed., Biotechnology in Public: A Review of Recent Research, London: Science Museum for the European Federation of Biotechnology, 1992; National Science Board, Science & Engineering Indicators – 1996, Washington, D.C.: U.S. Government Printing Office, 1996; U.S. Congress, Office of Technology Assessment, New Developments in Biotechnology – Background Paper: Public Perceptions of Biotechnology, Washington, D.C.: U.S. Government Printing Office, May 1987; and B. Zechendorf, "What the Public Thinks About Biotechnology – Better than Synthetic Food, but Worse than Organ Transplantation – A Survey of Opinion Polls," Bio/Technology, 1994, 12: 870-875.

[122] See Betsy Hanson and Dorothy Nelkin, "Public Responses to Genetic Engineering," Society, 1989, 27, 1: 76-80.

basic biotechnological tools. Once the potency of recombinant DNA, for example, had been demonstrated experimentally and a horizon of possible consequences began to come into view, the risks and potential benefits of implementing this new technique were roundly discussed and debated by scientists and policy-makers.[123] Reviewing this course of events from the distance of the mid-1990s, Paul Rabinow observed that by 1983, "[a] corner had been turned. The safety issue had been contained. Government regulators, Congress, business, and a significant sector of the scientific community were satisfied."[124] There remain still many gaps and inconsistencies within and across local, state, national, and international regulatory and legal standards.[125] For scientists, industrialists, and critics of biotechnology alike, these are sources of frequent or enduring consternation. But while procedural uncertainties have not, of course, been eliminated, and many ethical questions remain murky in the abstract, research involving the manipulation of living things is today conducted within a fairly stable, if not well-integrated, policy environment. The regulation of biotechnologies now has a history. Changes are instituted incrementally. Research

---

[123] For reports on the early history of regulatory policy formation in the scientific community, academic institutions, and local, state, and federal governments, see Sheldon Krimsky, Genetic Alchemy: The Social History of the Recombinant DNA Controversy, Cambridge, MA: MIT Press, 1982; and Susan Wright, Molecular Politics: Developing American and British Regulatory Policy for Genetic Engineering, 1972-1982, Chicago: University of Chicago Press, 1994. Similar policy debates are currently addressing the implications and possible dangers of stem cell research and human cloning. In July 2002, President Bush and a committee For an overview of the positions staked out by politicans, scientists, bioethicists, industrialists, academic administrators, and others, in debates on these issues, see William Kristol, and Eric Cohen, eds., The Future is Now: America Confronts the New Genetics, Lanham, MD: Rowman and Littlefield, 2002.

[124] Paul Rabinow, Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press, 1996, p. 25.

[125] For thorough discussions of policy in various jurisdictions, see Cliff Jernigan, High Tech Survival: The Impact of Government on High Tech and Biotech Companies, Woodside, CA: Olive Hill Lane Press, 1996.

and development practices are validated or reshaped in a more or less orderly fashion through settled mechanisms of policy determination, and against an established body of legal interpretations.

Still, critics in the academy and beyond continue to question the adequacy of enacted formal safeguards, and the mores, philosophical principles, and economic and political interests that these rules are said to express or reflect.[126] There are fears that scientists, businesspersons, and policy-makers dazzled by prospects of profits, returns on investments, and economic growth will allow the development of biotechnologies to proceed at the expense of human values and environmental safety.[127] Environmentalists' complaints and warnings often coincide with critiques of capitalism and the global political economy of biotechnology. Much has been written in the social sciences and the popular press about possible undesirable impacts of biotechnological development, particularly in agriculture, on economic and environmental conditions in both the First and Third Worlds. Critics have predicted

---

[126] Some consider biotechnological progress within expansive critiques of science, technology, and Western culture in general, e.g., Evelyn Fox Keller, Refiguring Life: Metaphors of Twentieth-Century Biology, New York: Columbia University Press, 1995; Donna J. Haraway, Modest-Witness@Second-Millenium, FemaleMan-Meets-OncoMouse: Feminism and Technoscience, New York: Routledge, 1997; and Vananda Shiva, Biopiracy: The Plunder of Nature and Knowledge, Boston, MA: South End Press, 1997.

[127] See, for example, Lawrence Busch, William B. Lacy, Jeffrey Burckhardt, and Laura R. Lacy (eds.), Plants, Power, and Profits: Social, Economic, and Ethical Consequences of the New Biotechnologies, Cambridge, MA: Basil Blackwell, 1991; Daniel Charles, Lords of the Harvest: Biotech, Big Money, and the Future of Food, Cambridge, MA: Perseus, 2001; Cary Fowler and Patrick R. Mooney, Shattering: Food, Politics, and the Loss of Genetic Diversity, Tucson, AZ: University of Arizona Press, 1990; Jack Ralph Kloppenburg, Jr., First the Seed: The Political Economy of Plant Biotechnology, 1492-2000, Cambridge: Cambridge University Press, 1988; Sheldon Krimsky, and Roger Wrubel, Agricultural Biotechnology and the Environment: Science, Policy, and Social Issues, Urbana, IL: University of Illinois Press, 1996. See also Jane Rissler and Margaret G. Mellon, The Ecological Risks of Engineered Crops, Cambridge, MA: MIT Press, 1996; Alan Russell and John Vogler, eds., The International Politics of Biotechnology: Investigating Global Futures, Manchester: Manchester

that the expropriation and monopolization of natural resources by large corporations and advanced industrial nations will reinforce global inequalities, threaten existing biodiversity, increase the likelihood of ecological accidents, and inhibit regional efforts to develop sustainable systems of agriculture and eradicate poverty and hunger. Many holding to these views are afraid that even if cures for dread diseases, increased crop yields, and other goods are delivered as promised, they may not be worth the price.

AN ODD MIXTURE OF SUSPICION AND FAITH

So, the technological and organizational innovations engineered by life science entrepreneurs have been applauded by some and criticized by others, but they certainly haven't been ignored. In fact, the biotech industry has garnered so much attention and generated so much talk about miracles and catastrophes of various kinds that observers occasionally associate the word 'biotechnology' with the word 'hyperbole.'[128] Free market crusaders argue vociferously that current regulatory restrictions on the testing of biotechnologies are overly stringent, unfair, and irrational, based not on sound scientific principles, but rather ignorance and fear.[129] Others believe that advertisements of biotechnological wonders in the popular press and on Wall Street

---

University Press, 2000; Rachel A. Schurman and Dennis Doyle Takahashi Kelso, Engineering Trouble: Biotechnology and Its Discontents, Berkeley, CA: University of California Press, 2003.

[128] See Laurie P. Cohen, "Some Biotech Firms Excel at State-of-the-Art Hype: Press Releases from Start-Up Biotechnology Firms," Wall Street Journal 13 March, 1992: C1; Robert Teitelman, Gene Dreams: Wall Street, Academia, and the Rise of Biotechnology, New York: Basic Books, 1989; Profits of Science: The American Marriage of Business and Technology, New York: Basic Books, 1994, ch. 10.

[129] See, for example, Henry I. Miller, Policy Controversy in Biotechnology: An Insider's View, Austin, TX: R.G. Landes, 1997.

have produced unrealistic expectations. Reports on progress in academic and pharmaceutical laboratories regularly refer to things like 'magic bullets' and 'medicines of the future,' suggesting that major breakthroughs in the treatment of disease are imminent. According to Dorothy Nelkin, such optimistic forecasts, backed by scientific authority, "raise hopes of instant cures." The public expects results, but growing bodies of biological and genetic knowledge have so far done litte more than to leave medical researchers in "a state of enlightened impotence."[130]

Still, even if fault is sometimes found with the organizations and institutions that conduct, regulate, or promote research on biotechnologies, faith in the instrumental potential of these tools and in the efficacy of the sciences that produced them remains, by every indication, undiminished. The National Science Foundation's biennial surveys indicate that public trust in the scientific community is not overwhelming – only 38% express "high confidence." Yet, 86% of those surveyed in 2001 agreed that "science and technology are making our lives healthier, easier, and more comfortable," and 85% agreed that "thanks to science and technology, there will be greater opportunities for future generations." [131] This faith in science is plainly evident in public conversations that make up U.S. political culture. For example, the White House, since the early 1990s, has touted the nation's biotech industry, nearly without reservation, as a source of wondrous future economic and medical improvements. In 1996, M.R.C. Greenwood and Rachel Levinson, Clinton

---

[130] Dorothy Nelkin, "Covering Gene Therapy: Beware the Hype (Promotional Rhetoric Used by Scientists Can Fail to Deliver)," Quill, 1996, 84, 7: 34-36; quotes on p. 36.

[131] See National Science Board, Science & Engineering Indicators - 2001, Washington, D.C.: U.S. Government Printing Office, 2001.

administration executives at the White House Office of Science and Technology Policy, confidently asserted that "biotechnology offers great promise for the future and has the potential to affect nearly every facet of our lives."[132] The Clinton administration pledged support for legislation that would encourage diversified sources of financial sponsorship for scientific research, tax policies that would provide incentives for high-tech investment, and public understandings of science. This broad pro-technology stance included express commitments to biotechnical expansion and 'rational' regulatory policies.

The Bush administration has adopted a similar posture regarding bioscience policy. Shortly after taking office, the president addressed bioindustrialists in San Diego and vowed to promote investments in commericial biotech projects, while promising additional funding for the National Institutes of Health. The speech expressed appreciation for the economic and therapeutic value of contemporary biomedicine: "We must continue to support the scientific research that has made the United States the world's leader in developing new disease treatments and cures." Bush also endorsed biotechnological approaches to improving agricultural yields: "With more than 800 million people in the world suffering from malnutrition, biotechnology offers enormous potential for farmers in developing countries to grow more food on less land."[133] After 9/11, the president's strategy for counterterrorism

---

[132] M.R.C. Greenwood and Rachel Levinson, "Expanding the Horizons of Biotechnology in the Twenty-First Century," pp. 233-245 in Biotechnology: Science, Engineering, and Ethical Challenges for the 21st Century, eds., Frederick B. Rudolph and Larry V. McIntire, Washington, D.C.: Joseph Henry Press, 1996, p. 244.

[133] See Mike Freeman and Thomas Kupper, "Bush Offers Upbeat Message – He Pledges to Support Steady Flow of Funds for Research, Development," San Diego Union-Tribune, June 26, 2001.

and homeland security included a bioscientific piece – in July 2004, Project Bioshield was approved by Congress and signed by Bush into law. The legislation authorized $5.6 billion over ten years for the development and distribution of vaccines and antidotes against smallpox, anthrax, botulin toxin, the ebola virus, and other possible agents of bioterror, and treatments for exposures to chemical and radiological weapons. Project Bioshield represents a boon to the biotech industry.[134] President Bush has asked the public to place their trust and their tax dollars with the life sciences. He expects the public to be as impressed with biotechnologies as he evidently is – in reaching out to biotechnologists for support, Bush has announced: "My administration is committed to working with your industry so that the great powers of biotechnology can serve the true interests of our nation and mankind."[135]

It is true that while Bush continues to promise advocacy for biotechnology and the biotech industry, his stance on basic stem cell research has not pleased scientists or bioindustrialists.[136] After publicly contemplating a ban on federal funding of research involving stem cells extracted from human fetuses, he ruled that government money could be dedicated to stem cell projects, after all, provided that investigators make use of existing cell lines only.[137] Many in the country's scientific community have warned

---

[134] William Branigin, "Bush Signs Legislation to Fight Bioterrorism: Project Bioshield Enables Government to Stockpile Vaccines, Expedite Research," Washington Post, July 21, 2004.

[135] White House, Office of the Press Secretary, "President Bush Urges Congress to Pass Bioshield Legislation," news release, June 23, 2003.

[136] "Administrations Stem Cell Stance Alarms Scientists," New York Times, January 31, 2001.

[137] Eric Cohen, "Bush's Stem-Cell Ruling: A Missouri Compromise," pp. 316-318 in The Future is Now: America Confronts the New Genetics, eds., William Kirstol and Eric Cohen, Lanham, MD: Rowman & Littlefield, 2002.

that this policy could jeopardize the leadership position of the U.S. in biological research, and saddle the domestic biotech industry with serious scientific and economic disadvantages.[138] There are strong feelings within the scientific community that the president's attitudes are anti-scientific. Yet, even Bush's moral reservations about stem cell research are premised on the capacities of bioscientists to enlarge the technological grasp of human beings. The assumption that the life sciences will continue to advance and eventually enable human beings to extend massively their control over biological processes lies behind statements forwarded, not only by both the most enthusiastic supporters, but also the staunchest opponents of biotechnological development. Jeremy Rifkin, for example, an outspoken critic of established institutional means of regulating the development and application of biotechnologies, says:

> The biotech revolution will affect every aspect of our lives. The way we eat; the way we date and marry; the way we have our babies; the way our children are raised and educated; the way we work; the way we engage in politics; the way we express our faith; the way we perceive the world around us and our place in it – all of our individual and shared realities will be deeply touched by the new technologies....[139]

Not so long ago, this was the stuff of science fiction. Today it is the stuff of practical projects. Useful applications for biotechnologies have not been manufactured and refined as quickly as once was expected. The motives and moral

---

[138] James Glantz, "At the Center of the Storm Over Bush and Science," New York Times, March 30, 2004. On a related bioscience policy matter, Bush has declared his flat opposition to human cloning experiments (while the scientific advisory commission he appointed suggested a more moderate 'wait-and-see' position). See Sheryl Gay Stolberg, "Panel Recommends a Moratorium on Cloning Research," New York Times, July 11, 2002.

character of the individuals and 'faceless' organizations conducting biotechnical work sometimes become objects of widespread speculation and suspicion. Yet, governments, large corporations, and private citizens continue to invest in the development of biotechnologies. Objections that various public constituencies raise to these investments, the specific projects that they underwrite, and the values that they are said to prioritize, are founded on like beliefs that attempts to develop biotechnologies will, in fact, have real and far-reaching consequences. The question is not whether biotechnologies will change the world in a multitude of ways, but rather whether all of these changes will be beneficial. It has not been my intention in this work to treat political contests over the control of biotechnological development in any substantial way, let alone to propose ways of resolving them. This study has been, however, about the emergence of an industrial ecology in which biotechnological research and development is conducted. This is a community characterized by its own conventions and practices that may be said, in a sense, to express or reflect a more or less coherent set of values. These values are not, however, properly understood as abstract ideals. They are rather intrinsic features of communal ways of life, ways of conducting science and business. These practices may, in fact, conflict with the interests and values of other social groups. There is no formula that can be applied to remedy such conflicts, but this empirical inquiry into the ways in which persons in the San Diego biotechnology community have conducted their business and understood

---

[139] Jeremy Rifkin, The Biotech Century: Harnessing the Gene and Remaking the World, New York: Jeremy P. Tarcher/Putnam, 1998, pp. 236-237.

their civic responsibilities may contribute to efforts to cast these problems into sharper relief.

In public and academic discussions of social problems associated with technical advances in the life sciences, the interests and values of biotechnologists and biotechnology companies are often simply assumed. Many outsiders commenting on the field are unfamiliar with these persons and the organizations to which they belong, and many others oversimplify or misrepresent in order to make their political or analytical points more forcefully. In order to remedy this situation, Paul Rabinow has investigated contemporary bioscience as a vocation in its new commercial settings, appropriately examining the norms that regulate this field of activity 'in context and process.' [140] He describes how the people, places, and things that make up commercial biotechnology – life scientists, their places of work, the techniques they employ, and the objects they produce – have been assembled, not by formal rational design (and so not as the expression of some abstract conception of value), but improvisationally, as a "contingent ensemble."[141] He finds that while pure commitments to 'traditional scientific ideals' are not in evidence, it would be a gross misrepresentation to say that biotechnologists are motivated predominantly by prospects of monetary gain: "Their scientific practice, they firmly believe, contributes to a general broadening of scientific understanding and technical mastery, to an eventual improvement of public health, and

---

[140] Paul Rabinow, Making PCR: A Story of Biotechnology, Chicago: University of Chicago Press, 1996; p. 14.

[141] Rabinow, Making PCR, p. 159.

even to the betterment of society. They are proud to have made something valuable."[142]

Many of the earliest academic participants in the biotech revolution have listed the desire to be of service to others among the leading motives behind their efforts to commercialize their research – in tones that make it difficult to doubt their sincerity. Herbert Boyer, reflecting on the criticisms, slights, and self-doubts that he endured after starting Genentech, and on the considerable contributions that the company made, in his estimation, at least, to science and society, remembers that: "...the money was not a driving factor. To me it was the excitement and challenge to do something like this. It was an opportunity to take the technology and the science to some pragmatic level....I always felt that what I was doing was right. I didn't think I was doing anything unethical or immoral." In San Diego, thinking about Hybritech's legacy, Ivor Royston expresses pride in the technical advances that his company made: "I'm sorry [Hybritech] didn't get into therapeutics, but I'm happy that it was able to make a contribution to medicine. The PSA test really revolutionized cancer care for men." Royston draws attention, in addition, to contributions that bioindustrialists have made to the city of San Diego: "I'm happy to be part of the biotech industry. We've created a lot of jobs in San Diego, made San Diego a better place. We're making it a clean business environment, there's no manufacturing pollution. It's kind of like wireless information technology. Biotech's pretty clean. It just needs a lot of water." Howard Birndorf also measures the accomplishments of the Hybritech alumni in

[142] Rabinow, Making PCR, p. 164.

economic terms: "Huge shareholder value was created by this original team."[143] But when asked, during his tenure as CEO of Nanogen, why he does what he does, Birndorf gave an answer that extended beyond purely financial concerns. Pointing beyond the door of his office, he included in his list of reasons personal obligations to the employees of his company: "I've got sixty people out there that depend on me doing it."

The biotech industry, like any other, will have to contend from time to time, and to greater or lesser degrees, with skepticism, mistrust, and even hostility from outsiders because biotech enterprises are profit-seeking entities. These attitudes may be warranted from time to time and to greater or lesser degrees because, inevitably, in certain instances, the profit-seeking behaviors of firms or persons will shade over into greed. The headline-making troubles of immunologist and former ImClone CEO Sam Waksal are an example. The ImClone scandal turned into a public relations fiasco for the biotech industry. Waksal was arrested and later convicted of insider trading after friends and family members sold huge batches of Imclone stock for many millions of dollars shortly before the FDA publicly announced its refusal to review the company's application for the regulatory approval of its lead drug candidate, a monoclonal-based anti-cancer agent called Erbitux. Waksal had been informed by the agency that the ruling was likely.[144] After Waksal's arrest, a Time magazine story described his jet-set lifestyle – which featured a personal art collection including works by Chagall and

---

[143] Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, Cambridge, MA: Perseus, 2000; p. 52.

[144] Andrew Pollack, "Ex-Drug Executive Faces Charges of Insider Trading," New York Times, August 8, 2002.

Picasso, personal debts amounting to $80 million dollars, regular tennis matches with financier Carl Icahn, parties for celebrity guests like Mick Jagger, Mariel Hemingway, and Martha Stewart– as well as his alleged securities violations.[145] The article painted a vivid portrait of a scientist succumbing to the temptations of lavish wealth in a spectacular manner. The question, of course, is 'How representative are cases like this one?' The answer, it appears, is not very. There is little evidence to suggest that fraud and scientific misconduct are more common in the biopharmaceutical industry than they are in academic settings, or anywhere else.

The FDA announced the approval of Erbitux in a March 2004 press release. The drug is being distributed by Bristol Myers. In its first few months on the market, it averaged about $25 million per month in sales. The drug works by sending monoclonal antibodies to bind and block growth factor receptor sites on cancer cell surfaces. The goal, in effect, is to starve and inhibit the growth of tumors. The idea for this approach, and the chimeric monoclonal antibody (called C225) designed to do the job, were originally developed by two UCSD researchers – John Mendelsohn and Gordon Sato. Mendelsohn is now president of the M.D. Anderson Cancer Center in Houston. He is the man who hired Ivor Royston to the faculty of the UCSD School of Medicine in 1977. Mendelsohn began experimenting with monoclonals in San Diego in the early 1980s, after Royston arrived and started Hybritech.[146] In a report on his

---

[145] Daniel Pollack, "Sam's Club," Time, June 24, 2002; p. 48-51. The FDA decision was based on problems with the design of the Phase III clinical trials of the drug. Patients treated with Erbitux also received standard chemotherapies. According to the FDA, this made it impossible to assess the efficacy of the experimental therapy. The agency has since concluded that the drug is, in fact, efficacious.

[146] Mendelsohn and Royston did a bit of collaborative work at UCSD. See, for example, R.O. Dillman, J.C. Beauregard, J. Mendelsohn, M.R. Green, S.B. Howell, and I. Royston, "Phase I trials of Thymosin

involvement with ImClone and clinical trials of Erbitux, Katherine Uranek states: "A review of 700 pages of documents indicates that [Mendelsohn] scrupulously followed the rules when he disclosed his financial interests in the monoclonal antibody C225 to the public and to the journals in which he published..." and "among colleagues, Mendelsohn has a reputation for forthrightness."[147] By all appearances, Mendelsohn is squeaky clean.

Gordon Sato was a well-known cell biologist at UCSD, and a member of the National Academy of Sciences. Walt Desmond, one of Hybritech's earliest cell biologists, worked as a postdoc in Sato's laboratory before moving to the monoclonal start-up in 1978. Sato made his contributions to the C225 project in 1983. He is listed as a co-inventor on the patent.[148] He retired from science in 1992, and has since been spending much of his time in the drought-stricken East African country of Eritrea, constructing fish farms and planting mangrove trees along the coast of the Red Sea, as sources of food for cattle and people. According to a New York Times story, Sato, as a co-inventor of Erbitux, could receive several hundred thousand dollars a year in royalties from sales of the drug. When informed that he might be receiving some

---

Fraction 5 and Thymosin 1," Journal of Biological Response Modifiers, 1, 1982: 35-41; J. Mendelsohn, R.O. Dillman, and I. Royston, "Use of biological response modifiers in the management of cancer," pp. 167-193 in Management of Advanced Cancer, eds. P. Periman and Favlol, Milan, Italy: Masson Publishing Co., 1983; R.E. Sobol, R.W. Astarita, C. Hofeditz, H. Masui, R. Fairshter, I. Royston, and J. Mendelsohn, "Epidermal growth factor receptor expression in human lung carcinomas defined by a monoclonal antibody," Journal of the National Cancer Institure 79, 1987: 403-407.

[147] See Katherine Uranek, "Balancing Business and Science at Imclone: Researchers in Business Struggle to Manage Conflicts of Interest," The Scientist, December 9, 2002, 16, 24: 54.

[148] John Mendelsohn, Tomoyuki Kawamoto, Gordon Sato, and Denry J. Sato, "Hybrid cell lines that produce monoclonal antibodies to epidermal growth factor receptor," U.S. Patent 4,943,533; filed March 19, 1987; issued July 24, 1990.

checks, he said, "I hope so, because I'm running out of money here."[149] Sato has reportedly spent about half a million dollars of his own money on his personal crusade in Africa. There is always a bottom line in business, and there are sometimes crooks, but there is little in the history of the biotech industry to suggest that greed, dishonesty, or irresponsibility are defining characteristics of bioentrepreneurs or researchers who take stakes in private ventures, or that unmanageable conflicts of interests characterize the practice of commercial bioscience.

Life scientists, whether working in ivory towers or industrial labs, are not, as a group, paragons of special virtue, but, as the story of Hybritech and its begattings illustrates, it is no simple matter to sum up the moral disposition of the activities in which they are engaged. In this regard, the development and use of biotechnologies appears to be no different than any other walk of life. What does set biotechnologists apart, however, is the fact that they have successfully established belief in the special technical efficacy of what they do. How they have cultivated this belief has been one of the principal topics addressed in the preceding chapters. It is beyond the empirical scope of this investigation to account for the generalized faith in the power and promise of science and technology that appears to be a secure feature of modern Western culture. This work has, however, examined how biotechnologists have sought to promote particular scientific and technological projects in particular social and historical contexts. Because it has, it can be described as, among other things, a portrait of the actual moral and ethical character of the sciences and scientific entrepreneurship in contemporary society.

---

[149] Andrew Pollack, "A Drug's Royalties May Ease Hunger," New York Times, March 7, 2004.

XII. ELI LILLY AND THE ROUTINIZATION OF CHARISMA

We're Lillyputians now.

The Magic Bulletin, Hybritech Employee Newsletter

THE MERGER

1985 was a turning point for Hybritech and the San Diego biotechnology industry. Hybritech had been very fortunate during its first seven years in business. It had been good, it had been lucky, and it had successfully entered diagnostics markets as an entrepreneurial start-up with an innovative technology. That much was not so unusual. The diagnostics industry had been regularly welcoming new entrants with new classes of products. Hybritech was different, however, in that it utilized a technology invented by academic biologists, it had been founded by academic entrepreneurs, and it was staffed by scientists who came out of high profile institutions of academic research. In addition, Hybritech had raised many millions of dollars in venture capital, and had become a public company in just its third year in operation, when it still had yet to see its first profits. The firm had expanded so rapidly that it was already preparing to go head-to-head in market competition with industry giants like Abbott, and the giants were evidently nervous about it.[1] And, what is more, the company had announced its intention to develop pharmaceuticals, too. No one had ever seen a business like this before.

Still, despite all of its successes, the company had run into trouble. Its convulsive growth and the ambitious reach of its development projects had generated

[1] See Warren Froelich, "Mighty Abbott, Little Hybritech Locked in Legal Battle," San Diego Union, March 18, 1985, p. B-1.

for the firm's executive committees a set of unfamiliar problems. Hybritech was in uncharted waters. The once diminutive science-driven start-up now employed hundreds. It was well on its way to becoming a mature industrial manufacturer, but the operation continued to depend on the innovative development of a new biotechnology, and nobody involved in the process was certain about how to proceed. The firm was experiencing difficulties of many different sorts – technical, commercial, and organizational. The biggest problems of all, perhaps, were financial. The company's R&D expenditures were enormous. Hybritech's spending was continually on the verge of spinning out of control. In a 1985 interview published in Business Week, Ted Greene admitted that the company was a "black hole into which money is pouring."[2] The idea of assembling a diagnostics operation in order to support research in therapeutics had sounded good when Kleiner Perkins came up with it and Greene later put it to paper. The strategy hadn't exactly failed, but when clinical progress turned out to be far more arduous than anticipated, some at the company began to entertain doubts. They wondered how long the firm's research could be sustained. Later, from a distance, in 1993, Howard Birndorf reflected on the approach: "It may not be the way to finance drug development," he said. "It's tough to support two large programs that are so different."[3] Those thoughts were beginning to dawn on Hybritech when Eli Lilly showed up in the summer of 1985 with an offer to shelter the

[2] Quoted in Dan Berger, "Hybritech Brings $330 Million; Lilly Buys S.D. Firm, A Leader in Biotechnology," San Diego Union, September 18, 1985, p. A-1.

[3] Craig D. Rose, "Magic Bullet That Missed: Hybritech Did a Lot Right, But Lilly Pulls Plug on New Drugs," San Diego Union-Tribune, October 26, 1993, p. C-1.

young firm and nurture its experimental programs. The board of directors decided that the time had come to sell the company.

This concluding chapter is about the sale of Hybritech to Eli Lilly, and the aftermath of the merger. At Hybritech, the deal meant (after a transitional period) an end to the organizational tumult that the company had experienced over the course of its development, but also the final demise of the entrepreneurial spirit that had characterized the firm through its infancy and adolescence. Beyond the boundaries of the firm, the acquisition would produce a kindling in the expansion of the San Diego biotechnology industry. Lilly first approached Hybritech to discuss a merger in October 1984. It seemed like a perfect match – Hybritech had the technology, and it was skilled, but starved for cash; Lilly wanted the technology, and could afford to purchase it. Its pharmaceutical business generated mountains of money. The talks were kept secret. Ted Greene and Hybritech CFO Tim Wollaeger traveled to San Francisco for a preliminary meeting with representatives from Lilly. According to Wollaeger, the Indianapolis contingent proposed a site away from San Diego because they would be traveling on a corporate jet, and "they didn't want people spotting their name on the tail of the airplane." Wollaeger describes the meeting as a friendly but mostly vacuous talk between Greene and Gene Step, president of Lilly's powerful pharmaceutical division, "sort of a 'someday this will all be ours together,' kind of thing, and 'Tim, can you work out the details?'" When the bargaining began in earnest, it wasn't clear that Tim and his VP of finance counterpart at Lilly, Jim Cornelius, would, in fact, be able to work out all of the details. The talks remained confidential. Few in addition to the participants learned about them.

The negotiation process was an on-again, off-again affair that dragged on for nearly a year and a half. The point of contention was the valuation of the young biotech company. During 1984, Hybritech's stock price had fluctuated between $11 and $22.75 per share. By February 1985, Lilly indicated that $20 per share was its best offer. Greene believed that this figure grossly undervalued the company. He wanted $30 per share. In Wollaeger's opinion, the discrepancy appeared because, in estimating what Hybritech might be able to achieve, Lilly discounted what the start-up had already accomplished: "Lilly never thought there was much value in the diagnostics business that we had. They were more interested in the imaging and therapeutics aspects."[4] There was a great deal of uncertainty attached to that part of the investment, and, to assess risks, Hybritech and Lilly started from different presuppositions regarding the young firm's capacities to push injectable products through expensive and time-consuming development, clinical testing, and regulatory approval processes. Hybritech had never done this before. Lilly had, and the big company knew how complex and difficult it could be. Not surprisingly, the two sides produced radically divergent forecasts of Hybritech's future performance and prospects. Greene projected a business worth $1 billion by 1992. Lilly thought half of

[4] Some observers who took the opposite approach and defined the company in terms of what it had already accomplished (and perhaps placed less stock – literally and figuratively – in Hybritech's therapeutics R&D program), expressed puzzlement over the acquisition. Steve Zimmer, for example, a New York biotechnology market analyst, stated, in an October 1985 interview with Genetic Engineering News: "I can't see why they (Lilly) acquired an immuno-diagnostics company since they have maintained for the last 10 years that they didn't want to get into this." Quoted in Dan Berger, "Lilly, Hybritech Merger Plan Stalls, Talks Continue," San Diego Union, December 14, 1985, p. E-1.

that figure by 1995 was a more realistic guess.[5] The sides were too far apart. Negotiations were suspended.

Almost immediately, Hybritech's value in the stock market began to climb, along with the rest of the biotech sector, following news of product approvals and clinical trial successes around the industry. By April, the company had devised an alternative plan for funding its programs. Says Wollaeger, "We had decided that we needed to go out and raise more money in the public markets. We actually sat down and started drafting documents to do it. I don't know if we told Lilly we were doing it, but they found out. The minute they found out we were going back into the public markets, they came back after us." Talks resumed. They went on for several more months, and, in the final days of summer, an agreement was reached. Lilly would purchase Hybritech for $29 per share. For each piece of Hybritech, shareholders would receive $22.00 in cash or Lilly convertible notes, and a warrant to purchase Lilly stock at $75.98 per share at any time through March 31, 1991. Both the buyer and seller were satisfied that the warrants would sell on the market for about $4.00. Hybritech investors would also receive one contingency payment unit (CPU) per share, a security that was to be listed on the American Stock Exchange, and was expected to trade initially at $3.00. Returns on the purchase of a CPU would depend on Hybritech's performance through December 31, 1995. They would be realized as annual cash payments determined according to the following formula:

- 6% of Hybritech's sales, plus
- 20% of the company's gross profits, less

[5] Lilly evidently didn't believe that Hybritech would be able to develop a therapeutic product by 1988 as Greene had estimated.

- a deductible starting at $11 million in 1986 and increasing at a compound rate of 35% each year through 1995, divided by
- the total number of shares of Hybritech common stock outstanding as of January 2, 1986 (about 13 million).[6]

After the cash, the warrant, and the CPU were summed, the price tag on each share of Hybritech came to $29. It was impossible to calculate what the real cost to Lilly would be. That would depend on Lilly's market value over time as purchases of the company's stock were made with the warrants, and on Hybritech's future profit and loss statements. It was plain, however, to the financial analysts who examined the terms of the agreement that Lilly was giving up well over $300 million. The deal was complicated, but it provided means of aligning the interests of the two companies even as they held to differing expectations regarding Hybritech's development potential, manufacturing capabilities, and future profits."[7]

Until just a few days before the announcement of the sale, on September 18, 1985, the only people at Hybritech who knew fully what was going on were the members of the board and a select group of senior managers. Knowledge of the transaction was restricted to those involved in sorting out the dense tangle of legal and financial issues that attend corporate acquisitions.[8] For all of the dollars at stake, it was a very small circle of decision-makers. Cole Owen believes that Ted Greene was the principal architect of the deal:

---

[6] Hybritech Proxy Statement-Sale Prospectus, February 14, 1986. The trade of CPUs meant that individuals could continue to invest in Hybritech without purchasing stock in Lilly.

[7] Tim Knepp, "Eli Lilly's Inventive Contingent Payout Proves a Good Prescription for Hybritech," Buyouts & Acquisitions, May/June 1987, pp. 10-15, 37.

[8] Carlee R. Scott, "Eli Lilly & Co. Agrees to Buy Hybritech Inc.; Drug Company Will Pay More Than $300 million to Get Into Diagnostics," Wall Street Journal September 19, 1985, p.8.

> Every rooster that crows takes credit for the sunrise, and there are a lot of roosters around relative to that Lilly deal. Ted was the person who did that Lilly deal. Anyone else who pretends that they had something to do with it...a lot of people had something to do with it, but Ted was the driver. Tim Wollaeger was involved. I think it was David [Hale], as well, but I think that the person who really deserves credit for the structure, arrangement, and getting to the endpoint, was Ted.[9]

Larry Respess, Hybritech's general counsel, also participated. His role was to examine the implications of Hybritech's corporate partnerships for the merger, and to assist with the valuation of the firm's intellectual properties. "I was one of the people who had to be involved," says Respess, "because there's a lot of due diligence that a company like Lilly would do on patents and other things that affected the legal department." The company's middle managers and chief scientists weren't informed until just a few days prior to public notification. Walt Desmond remembers, "Our level of management was in on it ahead of time, but not very much. It was a real business deal." For everyone else employed by, invested in, or otherwise involved with the company, the merger was a surprise. Most learned about it on the day of the press release. Few suspected that any important change was in the works. Sam Halpern, Hybritech's clinical associate at UCSD, claims to have figured out what was going on shortly beforehand when he called the company to talk to his scientific collaborators. He says that he first asked for Richard Bartholomew, but was told that he was out of town. He then requested to speak with Jim Frincke or Gary David. He was informed that they were out of town as well. Halpern asked where they had gone.

[9] Of his role in the acquisition, Wollaeger says, "I would never say that I did the important things in the Lilly deal, but I probably put in the most hours."

When he learned that all three were in Indianapolis, it occurred to him that they must be talking to Eli Lilly:

> All in Indianapolis? Why would all of the chief scientists be in Indianapolis? Then I thought, there is either a hostile takeover that they are trying to deal with, or there is a friendly acquisition going on, and what I need to do is go out and hock the house, get myself a hundred thousand dollars, and buy Hybritech like mad, because if a merger goes through, that's going to be worth a lot of money. I almost did it, but then I decided against it. I don't know why I decided against it. It had nothing to do with principles, because there wasn't any insider trading here. I figured out what was happening.

On September 18, Greg Payne was at work, in a laboratory at Hybritech, when he received a telephone call from his father: "My dad was a stockbroker, and he said, 'Hybritech's stock has stopped trading. What's going on?' And I said, 'I don't know.'" Within a few minutes, impromptu meetings were called in various places around the company, and the vice-presidents explained to the employees in their divisions what was happening. Payne was working in diagnostics R&D at the time, so David Kabakoff broke the news to his group: "I remember going out to the lobby, and Kabakoff announced that Lilly had purchased us. And everybody was pretty excited about it. Everybody thought it was a great deal." Kabakoff had put a positive spin on the news, as the management team had planned:

> I took my responsibility of selling my own organization on this very seriously, and we did a hell of a good job of creating enormous excitement. I don't think the Lilly management ever really gave us credit for how good a job we did of convincing Hybritech employees, and by then, it was a thousand or so people, that this was the greatest thing since sliced bread, OK? And I did that at the time with some real sincere views.

By September of 1985, the number of employees at Hybritech was approaching 1,000. More than half had been at the firm for less than two years. Many

of them considered Hybritech a desirable place to work. Biotechnology was new, commercial progress still depended on scientific exploration, and the firm's research teams enjoyed a great deal of autonomy on the job. For the technical personnel, at least, the working conditions were good. The science was exciting and challenging. Morale was high. But, of course, the latecomers didn't remember the trailers, they hadn't accrued substantial financial stakes in the enterprise, and they didn't feel any special allegiance, connection, or identity with the company. The place had become just too big for that. Consequently, the preservation of Hybritech's independence and distinctive culture was not a particular concern to most employees. Other issues took precedence. Walt Desmond recalls that when the acquisition was announced, the details of Lilly's dental, health, and retirement plans immediately became salient topics of conversation around the place. Hybritech employees assumed that Lilly's benefits package would be superior.[10]

Not everyone at the firm was thrilled by the announcement. "There were some," Desmond says, "who thought, 'Well, we were going to do it on our own,' and this was kind of a disappointment." Most of these were people who had been at Hybritech from its early days as a little start-up. The idea of being conscripted as foot soldiers into the army of a massive pharmaceutical corporation was a bit disorienting.

---

[10] Lilly's benefits were better, but, as it happened, Hybritech personnel weren't made eligible to enroll in the retirement plan right away. Hybritech had been planning, before the merger, to introduce its own 401(k) plan. After the merger was announced, Bill Crean, Hybritech's HR director, asked Lilly what to do. They instructed him to implement the original Hybritech plan, and that rollovers would be effected at a later date. According to Desmond, once the deal was finally consummated in March of the following year, and Lilly officials began traipsing through, Hybritech employees began asking at every opportunity, "'When are we going to get the retirement?'" Desmond also remembers the tenor of Lilly's answers: "One of the things that was always emphasized was that, as soon as you start making money, we'll talk about it."

Many were not sure what it would mean. Nevertheless, most of those who were initially hesitant about becoming 'Lillyputians' gradually became more open to the idea. Greene floated the notion that, as far as the day-to-day operation of the firm was concerned, nothing much would really change. He pointed out that Lilly had a good record in acquisition management, and cited the case of IVAC, a medical device manufacturer located in San Diego: "Lilly's philosophy is to allow their various individual businesses to run autonomously. Few people in San Diego know that IVAC is owned by Lilly. They let IVAC do their thing."[11] Greene suggested that, in order to preserve continuity in Hybritech's operations, and to enable the company to keep doing the wonderful job that had made it such an attractive acquisition target in the first place, Lilly would not meddle or interfere. It would stay out of the way.

Losing control was a natural worry at the upper levels of the organization, but the vice-presidents rationalized away their trepidation. David Kabakoff tells of reactions within the higher circles of management: "Many of us convinced ourselves that this was going to be the answer to how the company would get the resources that it needed to continue to develop and flourish, and that Lilly was going to treat us well. You went from some initial disappointment and skepticism to, 'Hey this is terrific.'" To the scientists and technologists, then, Hybritech's management portrayed the sale as an opportunity. The scientists were told that Lilly would make available a lot of

---

[11] Dan Berger, "Hybritech Brings $330 Million; Lilly Buys S.D. Firm, A Leader in Biotechnology," San Diego Union, September 18, 1985, p. A-1; Lilly purchased the company in 1977. In January 1994, when Lilly divulged its intent to sell Hybritech, it also announced plans to divest itself of IVAC and its other medical device subsidiaries. IVAC was sold at the end of the year to a San Diego start-up business called River Medical Inc. See Craig D. Rose, "Lilly Sells Hybritech; Beckman Buys Local Biotech, Plans Unclear," San Diego Union-Tribune, September 30, 1995, p. C-1.

money, and that research programs would be improved and enlarged. "So," says Gary David, "while it was a shock and really a disappointment, because we had expected to remain our own company...the important thing was to be able to do the research." Other responses to the announcement of the sale from people who had been around in the company's early days were not readily classified as either positive or negative. Russ Saunders, for example, had developed an ambivalent attitude regarding the progress of the company and his role in it some time before information about the merger began to circulate. The company's expansion had taken a toll on him personally, and left him indifferent to the big news: "I felt that Hybritech could make it on its own, but I was so beat up and tired at that point that I don't think I could have done it. I was just working like hell every day. I'd worked over the weekends, probably for three years.... I was organizing a department that was growing like crazy." Saunders had witnessed and made contributions to the maturation and success of the firm. He felt attached to Hybritech, friends that he had made, and operations that he had helped to build, but his first reaction to the appearance of Eli Lilly on the scene in September of 1985 was that it mattered only if he could finally take a break.

Before the sale could be completed, the Securities Exchange Commission had to review the conditions and consider the implications of the transaction, and give its permission (or not). The two companies had announced their intent to effect the change in ownership, and Eli Lilly had secured an option to purchase Hybritech according to the announced terms on or before December 31, 1985, pending approval by the SEC and Hybritech's shareholders. As the deadline approached with no word from the government, it became apparent that Lilly's option would expire before

Hybritech's shareholders could be convened to ratify the merger. Greene told reporters, "The SEC comment period took longer than we expected. Apparently, they wanted to take their time looking at the contingent payment unit security that is part of this deal. This is the first time, I believe, that such a security has been issued in the sale of a company."[12] The delay benefited Hybritech – in fact, the company realized something like an additional $40 million.

When the company's stock was suspended in September to inform the market of the merger, shares in Hybritech were selling for $26.75.[13] As trading resumed, the announcement gave the stock an added boost. At the same time, general demand for securities in the biotech sector continued steadily to increase. It was a good time to be in the field. Hybritech kept growing in value. By mid-December, the price had reached $31 per share. When Lilly saw that its option to buy would expire, it reasoned that, given the upward trend in the market, it made sense to renegotiate sooner rather than later, if it was going to stay in the deal. The price was upped from $29 to $32 per share.[14] An anonymous stock analyst said of Hybritech: "When the option ran out, they simply decided to hold Lilly up for more money."[15] The final provisions of the deal were hammered out in February and approved by Hybritech's shareholders on March 18, 1986. Less than eight years earlier, Hybritech, Inc. had been started by Ivor

---

[12] Michael Kinsman, "Hybritech Sale Price Goes Up," San Diego Tribune, December 18, 1985, p. A-35.

[13] Dan Berger, "Eli Lilly Fattens Bid for Hybritech: Value of Indianapolis Firm's Deal Placed at $392 Million," San Diego Union, December 18, 1985, p. F1.

[14] As the sale approached, Hybritech's stock rose above $35 per share, an all-time high for the company. See "Hybritech OKs Merger into Eli Lilly," San Diego Tribune, March 19, 1986, p. A-19.

[15] Dan Berger, "Eli Lilly Fattens Bid for Hybritech: Value of Indianapolis Firm's Deal Placed at $392 Million," San Diego Union, December 18, 1985, p. F1.

Royston and Howard Birndorf with a check from Kleiner Perkins for $300,000. Around the time of the acquisition, estimates of the sale price ranged from $350 to $480 million.[16]

"JUST LIKE WORKING FOR THE GOVERNMENT"

Before the acquisition was finalized, Lilly requested that Hybritech's top officers – Ted Greene and the vice-presidents – sign thirty-six month employment contracts. All except Cole Owen agreed to do so. The idea, ostensibly, was to maintain routines and avoid disruptions at the new subsidiary during the transitional period, as both companies cooperated to make any changes that were needed in order to bring Hybritech into the Lilly fold. The general plan called for Hybritech to keep its diagnostics business and its imaging and therapeutics R&D programs up and running, while working closely with the scientists in Lilly's newly-formed monoclonal antibody division. Many at Hybritech considered the plan sensible and workable. "My thoughts," David Hale remembers, "were that they didn't have a diagnostics business. They didn't have anybody in Indianapolis who really knew the diagnostics business. And they had told us that we would operate autonomously." Hale was the president of the company. He was in control, and it didn't appear that his authority would be compromised by the deal. He expected that life at Hybritech would continue much as it had before the sale.

It didn't. People who were present on the scene hold conflicting opinions about exactly what happened, but Hybritech was remade by its interactions with Lilly

---

[16] See "Eli Lilly Sweetens Bid for Hybritech to $374 million," Wall Street Journal, Wednesday, December 18, 1985, p.14; and Chris Kraul, "Hybritech Patent Upheld By Court, San Diego Union, September 23, 1986, p. E-1.

after the acquisition, and its organizational trajectory was altered significantly. The company's rates of technical innovation, organizational expansion, and commercial growth all tailed off. Some observers were convinced that Lilly's bureaucracy had strangled the creative young firm. Others believed that the company had been managed appropriately, and that its mediocre performance beyond the acquisition was due primarily to technical failures.[17] Looking backwards, some now suggest that Lilly simply pushed Hybritech further down rails it was already riding like a hellbound train, toward a logical endpoint, given the nature of the technical projects it had taken on, and conditions in the firm's various commercial, organizational, and institutional environments. Maybe Lilly just accelerated the pace. In any event, Hybritech had reached its high water mark with the purchase. Following the introduction in April 1986 of the company's diagnostic test for PSA (prostate specific antigen) – a huge success that had been developed before the merger and approved for sale by the FDA immediately afterwards – Hybritech began a long period of commercial stagnation and decline.[18]

---

[17] See Craig D. Rose, "Magic Bullet That Missed: Hybritech Did a Lot Right, but Lilly Pulls Plug on New Drugs," San Diego Union, October 26, 1993; p. C-1. There is nearly universal agreement regarding Hybritech's performance after the sale to Lilly, but very little coherence among explanations for it. This account is based on interviews with persons associated with Hybritech before the acquisition. It doesn't present views from the Lilly side, and doesn't purport to be an objective analysis or diagnosis of Hybritech's organizational problems. The chapter presents the opinions of some participants. It also describes what occurred subsequently in San Diego's biotech industry, partly, at least, because of the sale.

[18] PSA was first identified in 1970. See R.J. Albin, W.A. Soanes, P. Bronson, and E. Witebsky, "Precipitating antigens of the normal human prostate," Journal of Reproduction and Fertility 1970, 22: 573-574; R.J. Albin, P. Bronson, W.A. Soanes, and E. Witebsky, "Tissue- and species-specific antigens of normal human prostatic tissue," Journal of Immunology 1970, 104: 1329-1339. It was purified and characterized in 1979 by researchers at Roswell Park Cancer Institute in Buffalo, New York. See M.C. Wang, L.A. Valenzuela, and G.P. Murphy, "Purification of a human prostate specific antigen," Investigative Urology 1979, 17: 159-163. Ivor Royston recalls Hybritech's decision to develop a PSA

Lilly had assured Hybritech's leadership that the firm's established routines wouldn't be significantly affected by the acquisition. Presumably, the promise was sincere, but many changes took place nonetheless. The 'Lilly way' began to be instituted at Hybritech. The process commenced with a restructuring of the executive apparatus at the top of the new subsidiary – despite the employment contracts that had been signed. Ted Greene was the first to go. He resigned in October 1986.[19] In retrospect, given Greene's history, temperament, and role as CEO and chairman at Hybritech, it was perhaps predictable that his tenure as an employee of Eli Lilly would be brief. Wollaeger speculates that, "Ted was probably told [by Lilly executives], you know, 'We want you to write some big strategic plan, but David Hale's going to run day-to-day operations, and you can be some kind of advisor to the top management of Lilly.'" Whether Greene elected freely to leave Hybritech or was forced out, his resignation was no great surprise to anyone familiar with the company and the circumstances of the acquisition. In fact, Wollaeger wonders whether Greene hadn't planned his departure from the outset of the Lilly deal: "I've never gotten him to tell me that. I'm not sure I've ever asked him."

Wollaeger was the next Hybritech executive to take his leave. As he tells it, there's no question about whose idea it was: "They basically fired me, which was odd, because I had a three-year employment agreement that they had pressured me, five months before, to sign." The contract gave him a good deal of leverage in

---

kit: "I believe Gary David gets credit for that. I remember him saying, 'You know, I think I can get the PSA antigen out of Roswell Park,' where it was just described in a paper."

[19] Chris Kraul, "He Wants to Duplicate Story of Hybritech," San Diego Union, October 23, 1986, p. C-1.

negotiations on a severance compensation package. "I worked them pretty hard on it," he says, "and got a nice financial deal." Wollaeger claims that his dismissal was a surprise, but Cole Owen suggests that perhaps it shouldn't have been unexpected: "A small company needs a chief financial officer, but not after it's a subsidiary of a pharmaceutical company. You need a good controller, but you don't really want a CFO. You don't want them making independent decisions about what they're doing." Life as a wholly owned subsidiary is different than life as an independent company. It just doesn't make sense and it's not really possible for a business organization to operate after a merger in the same manner as it did beforehand. Hybritech had to go through a series of adjustments as its practices, interests, and modes of operation were gradually aligned with those of its parent company.

David Hale maintains that when Hybritech became part of Lilly, "The operating environment changed tremendously. Lilly's operating style was that all of the decisions are made, you know, kind of at the top of the pyramid. So, I think the operating style and the culture changed within the company pretty quickly." Hale started reporting to Indianapolis immediately after the acquisition, in March 1986. After several months of that, he says, "It became pretty clear to me that, you know, the environment was going to be a Lilly environment, not a Hybritech environment." When this reality started to sink in on Hybritech's upper management team, those who weren't enthralled with the Lilly environment began walking out the door. Tom Adams and Howard Birndorf had already departed two years earlier. Following Cole Owen, Ted Greene, and Tim Wollaeger to early exits after the sale, were Ron Taylor, Dennis Carlo, and Cam Garner. All left within a year. Only David Kabakoff and

Karen Klause stayed for the full three years of their employment contracts. With the defections, Hale says, "it became more difficult to operate." He was soon gone, too, by the end of May 1987.[20] The upper management group had split up and left. Lilly appointees took their places.

The transition was difficult at lower levels of the organization, too. Tina Nova, a company scientist, says, "I think the hardest part was we were all brought together after the acquisition and told that nothing would change, and then, of course, it changed." The firm was no longer struggling for survival, and its 'sense of urgency' began to dissipate. For the first time, displays of affluence were observed on the premises. Individuals holding substantial shares in the company had gotten rich, on paper, when the firm went public, and their wealth had increased as the value of the company ran up in the marketplace. It was no secret that some in the company were sitting on big gains, but the capital was tied up, and rarely mentioned. After the acquisition, many of these people were able, for the first time, to cash out. Hybritech's numerous millionaires had suddenly achieved liquidity. Nova joined the company in 1983, long after the big pieces of penny stock had been doled out. She had done important work on the PSA test, the kit that became the company's all-time best-selling product, but now, she hadn't much to show for it – just a little job working for big Eli Lilly – while others had profited handsomely. According to Nova, it was difficult for her and many similarly positioned within the company to ignore the visible evidence of wealth out in the parking lot:

---

[20] Craig D. Rose, "Hale Resigns at Hybritech; Stitle is Replacement," San Diego Union, May 8, 1987, p. E-1.

> It was hard. You know, it was real obvious to us scientists that a lot of people there had gotten really wealthy. We knew that it was a few, and that it was the people at the top, and it really wasn't the scientists, it was the administrators. Nobody really cared about that, but we saw a lot of new Porsches and Ferraris, and what have you, in the parking lot. So, we saw a lot of changes.[21]

It was difficult, under these conditions, for employees to sustain ideal commitments to the firm. Many who had felt that Hybritech was some special kind of place were forced to give up the illusion for good. Nova wasn't jealous of the new wealth, but she, like others, felt undervalued and left out. Gradually, it dawned on people that Hybritech had been fleeced – now that Lilly had purchased the firm, it was no longer a place of boundless possibilities. No one had ever gotten rich working nine-to-five for Eli Lilly. The company wouldn't be making any more biotech millionaires, and the cheers wouldn't be as hearty when announcements of technical progress or commercial successes were made at all-employee meetings. And when the company's leadership began to flee, many in the lower ranks expressed vague feelings of betrayal. A September 1987 column in The Magic Bulletin, the company newsletter, offered employees' observations of life after Lilly. The piece, authored by somebody called Auntie Bodyspecs, included quotes attributed to a former Hybritech notable. This personage, many at the company suspected, had taken the money and run:

> "I'm never going to let Hybritech be purchased by a large company."
>
> – Ted Greene, fall of 1985.

---

[21] David Kabakoff maintains that Hybritech's insiders weren't motivated to enter into the merger agreement by the chance to get their money out of the company. He says, "The fact of the matter is that stuff was close to converting anyway, whether we'd been bought out or not. It would have happened anyway. So, the financial piece of it, I mean that really ended up, in the scheme of things, not being particularly swaying to many of us."

"I don't know about you guys, but I'll be here a year from now."

– Ted Greene, after Hybritech acquisition.[22]

The attributions are a faux lament of abandonment, playful, but a bit rueful, too. Ted stole off with the magic, and left his friends stranded. And once the ties had been severed, some evidently questioned whether Ted had ever really been the friend they had imagined. Unease about the new situation wasn't relieved when the employees learned that David Hale's replacement would come from Indianapolis. Hybritech's next president and COO would be a Lilly interloper – Stephen Stitle, a corporate attorney, and president of Lilly's new monoclonal antibody division. Upon his arrival, Stitle sent mixed signals about the future that Lilly envisioned for its new acquisition. His statements regarding the small company's relationship with its larger corporate parent were vague: "Hybritech is distinct, but Hybritech will be better because of the support Lilly can bring to it.... When you've got over 4,000 scientists (as does Lilly) the opportunities are far greater than operating independently."[23] This kind of talk was unsettling rather than encouraging. If such numbers were important, the scientists and technicians in San Diego wondered, and if Lilly already possessed them, then why did the corporation need them? Why did it need Hybritech, and how would the biotech company remain 'distinct?' Stitle provoked further worries about Hybritech's autonomy and its status in Eli Lilly's empire when he announced that he wouldn't be moving to San Diego. He would serve only on an interim basis. Lilly's

---

[22] "Auntie Bodyspecs," The Magic Bulletin, September 1987, II, 5: 1.

[23] Craig D. Rose, "New President Charts Course for Hybritech; Indianapolis-Commuter Stitle Says Lilly Merger Beneficial," San Diego Union, July 19, 1987, p. I-1.

corporate jets would be making regularly scheduled visits to Southern California, but Stitle intended to act as Hybritech's president from his desk in Indianapolis. To many of those who had been thrilled to participate in Hybritech's free wheeling ascent, it seemed that the company was being slowly transformed into just another place to have a job.

As Lilly colonized Hybritech, it became apparent that there were significant differences between the established pharmaceutical corporation and the young biotech firm in terms of their general approaches to organizing people. Hybritech had been a model of flexible, post-industrial enterprise – agile and adaptive, and designed to respond rapidly to changes in its environment. Bill Crean compares Hybritech's mode of tactical maneuvering to conventional approaches engaged by large corporations: "We were fast to make decisions. We didn't have lengthy planning processes. In fact, our business plan was a one-year plan. Typically, they are three-to-five years. The Japanese have twenty-to-thirty year plans. It was hard for us to look past twelve months." As a subsidiary of Eli Lilly, however, Hybritech was obliged to accommodate its parent's interests in long-term scheduling, and to wait on the larger company's measured and far more cautious policy-making procedures. The small firm was now required to fit into a larger corporate scheme, and so, it had to learn how to think differently. Created by young scientists escaping the tradition-bound practices of academia, and young executives chasing opportunities previously unavailable in the pharmaceutical and diagnostics industries, Hybritech had embraced informality, openness, and managerial transparency as organizational ideals. This was at odds with Lilly's buttoned-down, hierarchical approach to internal affairs. The

difference in corporate attitudes became apparent in the way Lilly responded to certain peculiar customs that had emerged as constitutive features of Hybritech's new 'biotech' culture. The company's monthly all-employee meetings were a case in point. According to Bill Crean:

> David and Ted would sit down with all the employees in one room and say, 'Here's what went on last month. Here's where we won business, here's where we lost business. Here's what our market share is, here's what's happening in R&D. Hey, we've got a new 401k plan, we're going to hear a little bit about that,' and most companies didn't meet that frequently with employees.

This was something new to Crean, who, before coming to Hybritech, had spent considerable time in large corporations – Baxter International and American Hospital Supply. The practice was new to Lilly, too, but the big company didn't perceive much value in it. After Lilly arrived on the scene, the meetings continued, but they changed. They became less concerned with informing employees, especially about deliberations taking place at the executive level. They were soon reduced mostly to generic exhortations for enhanced productivity. TGIF parties were another Hybritech custom that Lilly didn't quite understand. Every Friday afternoon, at one or another of the company's sites, all employees would meet for beer and chips. People were able to visit with each other in friendly, informal circumstances. A fair amount of business was conducted during these gatherings, and they helped to smooth processes of intraorganizational communication and cooperation, but the Lilly people considered them mostly frivolous. The big company was conservative, and just didn't do things this way. The new managers from Indianapolis had a particularly hard time accepting alcohol on the campus, because of the risks to the employees, the risks to the

surrounding community, and the liabilities of the corporation if the employees overindulged. Bill Crean comments on the clash of attitudes:

> We had a flag with a beer mug on it, and we would hoist it on Friday afternoons. Out in front of Hybritech, there were three flags – an American flag, a California flag, and a Belgian flag, for our plant in Liege, Belgium. When Lilly saw the beer mug flag, that kind of did it for them. They said that they really wanted to put a stop to that right away.

Hybritech had been populated by young people, many of whom pictured themselves as iconoclasts, rebels, and secessionists – scientific and industrial expatriates. The firm had taken pride and pleasure in flouting the staid conventions of business and academic science. It hadn't reflected on its place in the life of the local community, or its obligations to residential and commercial neighbors. Eli Lilly and Company, in contrast, had been doing this for decades. The corporation was acutely sensitive to public perceptions and concerned always with maintaining appearances. Suggestions regarding propriety and civic engagement were conveyed from Indianapolis, conventions of community activism were imported, and, as headlines in The Magic Bulletin at the time illustrate, Hybritech began working to establish itself as a good corporate citizen:

"Hybritech Begins Volunteer Recycling Program."

"Holiday Food and Toy Drive Becomes an Annual Event."

"United Way Campaign: 'It Brings Out the Best in All of Us.'"

For Eli Lilly, community relations was a civic duty and an indispensable corporate function, and now that Hybritech was part of the family, it was expected to do its part as well. Other sections of the newsletter showed that Hybritech's hundreds

of employees were tying the company to San Diego in more intimate ways. The "MoAb Gab" column announced engagements, weddings, births, deaths, graduations, and so on – arrivals, departures, rites of passage, activities, and events of all sorts that defined people's lives apart from their jobs. The character of Hybritech's labor force had changed. In the beginning, most of the people at the company were itinerant academics or industrial managers, and most of them workaholics, either by natural inclination or in answer to the extraordinary happenings taking place within and around the firm. By 1986, however, the vast majority of employees were firmly rooted San Diegans who showed up at the company in order to make a living. They weren't necessarily consumed by science or business. In fact, for most, other things were more important and took precedence. Most employees were striving to achieve balance in their lives – between work and family, work and play, or work and voluntary associations. In its early days, Hybritech had been an experiment. The company was originally a project that some adventurous souls had decided to try out for a while. They assumed that if it didn't work, they would then return to more secure environs to seek employment. By the time Lilly took over, however, most Hybritech employees were preoccupied with establishing stable careers, supporting families, raising children, assuming mortgages, and so on. The "Kudos" section of The Magic Bulletin followed their progress in these pursuits. It announced promotions, a dozen or more in every issue. It included photographs of those moving to new stations, along with explanatory captions:

'to QA Inspectr II from QA Inspectr I;'

'to bookkeeper from A/R processor;'

'to Sr Res Asst I from Res Asst;'

'to Facilities Planner from Mechanic Coordinator;'

'to Matl Handler II from Matl Handler I;'

'to Production Chemist from Lab Asst IV'

Never was it mentioned that any of these persons had accomplished anything in particular on the job in order to earn their new stripes. They did as they were told and they were moved up. Hybritech had become an organization in which individuals advanced, not by making innovations or solving problems, necessarily, but rather by showing up and following the rules. It had become a stable, well-ordered place. The firm had started out as a playground for wayward scientists but it had become an institution that families depended on for their livelihoods. Ivor Royston recognized the kind of environment that had been produced by Hybritech's success and growth, and he believed that Eli Lilly was perfectly suited to administer it. He approved the sale of the company to Lilly precisely because the Indianapolis organization was so solid, stalwart, and structured: "Lilly can provide very nice security and is loyal to its employees. It's just like working for the government."[24] And, after a time, it became obvious that Lilly wanted to remake Hybritech in its own image, just as Royston assumed it would. The big company had assured the smaller one that it would be permitted to operate autonomously after the acquisition, but that apparently guaranteed only that Hybritech would continue to maintain its own separate profit and loss statement. Beyond that, Lilly began making adjustments as it saw fit to the

[24] Craig D. Rose, "New President Charts Course for Hybritech: Indianapolis Commuter Says Lilly Merger Beneficial," San Diego Union, July 19, 1987, p. I-1.

subsidiary's methods and means. The Indianapolis home office issued to San Diego definite instructions on how to adjust Hybritech's behavior and organization.

These adjustments were effected largely through personnel shifts and the implementation of various standards, policies, programs, and plans. Over time, Lilly people were sent from Indianapolis to San Diego with increasing frequency to fill managerial and scientific vacancies in the organization, at various levels. Greg Payne says, "Lilly, for a couple years, it seemed, used Hybritech as a training ground, sending out some of their young execs and saying, you know, 'Here, have at it. Play around.'" At the same time, Hybritech people traveled to Indianapolis to be enrolled in Lilly's management training programs. Lilly had been in business for over a hundred years. The corporation had devised numerous organizational techniques for grooming new management cohorts. At Hybritech before Lilly, there hadn't been any training programs. The company had, at first, hired all of its managers from outside. Later, the incessant expansion of operations forced the firm to start selecting candidates from its own ranks. Scientists started moving into managerial positions, but training consisted entirely of learning on the job. According to Payne, "It was just like 'sink or swim,' and 'here, you have to do it,' and some of them did it better than others."[25] After the merger, however, management education at Hybritech was comprised of numerous programs administered or approved by Indianapolis.

---

[25] Payne adds: "You know, just because you had a Ph.D. didn't mean you were any good at managing people. That's not to say that the scientists that we had at the very beginning weren't good supervisors, or weren't good managers. It was just that perhaps a lot of them didn't have any training in it." Some lacked interest in it, as well. Payne points to Gary David as an example: "Over time, he ended up getting more and more management responsibility, and then, actually, he kind of shed that, because he didn't want that. It kept him out of the science. And there were some that were that way. And to me, you know, if somebody's passion was really to be involved with science day-to-day, why make them a manager if they don't want to be? But then, you have to account for them. How are you going to

QUALITY BRAINCELLING

In August 1987, Lilly announced that Don Grimm, director of sales at its Western Division located in Pasadena, would be taking over as Hybritech's permanent president.[26] When the new executive arrived in San Diego, he set about 'reengineering' the company. An area in dire need of attention, Grimm saw, was manufacturing. Hybritech's operation simply wasn't up to pharmaceutical industry standards. The firm had managed its scale-up reasonably well for a small start-up working with a brand new technology, but there were numerous inefficiencies embedded in its processes. Hybritech's glaring weakness was Lilly's greatest strength. Lilly made money by cutting costs, by streamlining production and manufacturing, by operating as efficiently as possible on scales as large as possible. The pharmaceutical company employed some of the world's leading experts on biomedical manufacturing systems. So, when production people from Indianapolis came in and looked around Hybritech's facilities, they saw redundancy, waste, and

---

manage these people?" On joining the managers, David says, "I've probably repressed most of that. What I remember is Ted promising that I would always have thirty percent of my time in the lab, and eventually realizing that thirty percent of the time in the lab was useless – it was just enough to get frustrated because you could never carry anything to completion – and giving up. I would have rather stayed in the lab. The nice thing about being a manager is that you get involved in a lot of different things. I've always enjoyed getting involved in a lot of different things. On the other hand, I really like working with my hands. So, after having a taste of it, I probably wouldn't have been happy either way." Although David never found managing industrial scientists entirely to his liking, he did acquire definite opinions on how the job is best done, and who ought to be doing it: "I've seen an awful lot of people get pulled out of science into management, or intentionally go out of science into management, before they've had enough laboratory experience under their belts to be effective. You really need to have a gut feel for what goes on in the lab, not an intellectual feel for it. You need to be able to relate to the people who are in there doing the work, otherwise you end up pissing off a lot of people." In academic settings, senior scientists manage laboratories, typically after extended tours of duty in the trenches. It isn't always so in the biotech industry.

[26] "Lilly Names Grimm Chief of Hybritech," San Diego Tribune, August 11, 1987, p. AA-1.

confusion, and one of the first things that they wanted to do, naturally, was to show Hybritech how to run a proper manufacturing operation

The Hybritech folk could hardly disagree with Lilly's assessments. Gary David, along with just about everybody else at the firm at the time, concedes that the young company had a lot to learn. He says, "I have to be careful how I say this, because I might insult the shit out of manufacturing, but we were essentially a small company that was growing, and our manufacturing processes and our philosophies weren't quite growing at the same rate as our size." Scrap rates were high. Quality assurance and quality control procedures were inadequate. From the beginning, manufacturing had been a troublesome task for the biotech company to manage. Using a standard industry metric, David compares Lilly's manufacturing performance to Hybritech's: "Their baselines were pharmaceutical industry benchmarks, where COPS [cost of production sold] is about 30-35%. Ours was a factor or two or so above that. Ours was too high. It needed to come down." Grimm went to work on it. He was an affable man, but it became clear to Hybritech employees that he wasn't impressed or satisfied with the company, and that he meant to reorganize the place in the 'Lilly way.' He later ruffled feathers in San Diego's biotech community when he suggested that Hybritech had been "dysfunctional" when Lilly acquired it. "Hybritech," said Grimm, "was like a young teen-ager. There was lots of energy, lots of ideas, great science and the people were terrific. But the company needed to get through a maturation process that comes with age."[27]

---

[27] Craig D. Rose, "Magic Bullet That Missed: Hybritech Did a Lot Right, but Lilly Pulls Plug on New Drugs," San Diego Union, October 26, 1993; p. C-1.

In many American industries struggling to remain competitive in international markets during the 1980s, enlightened executives turned to the adoption of 'total quality management' (TQM) or 'business process reengineering' (BPR) programs. The pharmaceutical industry was no exception. Lilly approved of such initiatives, and all of the 'management solution' mantras of the era were chanted at Hybritech at one time or another. A little over a year into his tenure as president of the company, Grimm hired a Boston-based consulting firm, Organizational Dynamics, Inc. (ODi), to come to San Diego to teach the company about 'customer focus,' 'Pareto analysis,' 'flowcharting,' and 'action planning.' Quality soon became the word at the firm. It appeared everywhere – on the walls, in company documents, and in conversation. Under the guise of TQM, the home office set about teaching workers at the satellite about the crucial importance of eliminating or reducing mistakes, defects, scrap, excess inventory, unnecessary field service, customer returns and allowances, rush delivery costs, past-due receivables, customer dissatisfaction, and loss of business.

Lilly's efforts at reeducation included classes on topics such as 'Quality Management Skills' (QMS) and 'Hybritech Integrated Planning' (HIP), and the formation of 'teams' (i.e., quality circles), 'Hybritech Team Excellence' (HTE) and 'Quality Action Teams' (QAT), for example. It was perhaps a cruel trick to inflict TQM on the loosely hinged, innovative biotech firm. Still, holdovers from the former regime apparently endured it, and some of the company's young scientists, at least, took to corporate sloganeering as earnestly and enthusiastically as they had to their new IBM PCs. Occasionally, the rhetoric plumbed absurd depths. On March 17, 1989, a large hanging mobile, entitled 'Harmony,' was installed in the lobby of

Hybritech's Torrey Pines headquarters, as the symbol of 'Hybritech Team Excellence.' In the next issue of the company newsletter, members of the upper management team reflected on the meaning of the sculpture and its significance in the context of Hybritech's activities and endeavors. Karen Klause, the president of Hybritech Clinical Partners and vice-president of sales and marketing of the in vivo R&D division, contributed this:

> Harmony is the existence of peaceful tranquility in balance with a common theme. It symbolizes total agreement and mutual understanding, conformity and concurrence, and cooperation and flexibility in concert with an ultimate oneness. The harmonious ideals of a shared commitment and respect for the individual are embodied in the Mission Statement as our commitment to our employees, and the new mobile represents the ideal symmetry we can all strive to attain.[28]

Was this serious, or an ironic poke? In either case, its appearance in the newsletter indicated that, in just three years, Hybritech had become thoroughly imbued with Lilly's ethic of conformity, and also that, while the corporation expected displays of obeisance, it wasn't overly concerned with content. Other readings of the sculpture united form and substance anyway, and didn't beg for interpretive charity. For example, Chet Damecki, vice-president of operations, wrote, "The mobile symbolizes to me the delicate balance necessary to achieve teamwork and unanimity among the people, functions, and customers of Hybritech." He neglected to specify where in the sculpture the paychecks, rebates, and discounted terms were represented, but the ideology had been serviced.[29] Some members of the organization seem to have

---

[28] "Harmony Comes to Hybritech," The Magic Bulletin, April 1989, iv, 3, p. 9.

[29] Not everyone was with the program, of course. Some maintained a healthy detachment. Hybritech employee Michele Lifsey (not a member of the upper management team) joked that the mobile – or maybe the exercise of interpreting it – represented "a flashback from the '60s." Gary David added his

become completely submerged in companyspeak. In the same issue of the newsletter, Lou Schioppi suggested that a new kind of consciousness, a product of concerted quality awareness education, was becoming omnipresent within the firm. Schioppi reported that, "The impact of TQA training is evident everywhere at Hybritech. People walk into meetings and find contingency diagrams adorning unerased blackboards. Brainstorming has also become commonplace. Some people are practicing a particularly intense version of it called braincelling."[30]

Unfortunately, the braincelling did not result in dramatic technical leaps forward. Lilly improved Hybritech's manufacturing systems (particularly, says Gary David, in the area of antibody production: "They were the driving force that got us to move many of the antibodies into in vitro production. I think that was an important move. That did a lot of good"), but the refinements were purchased at a high cost to the company. They were achieved by wrenching the firm out of some conventional patterns to which it had grown accustomed. These weren't just comfortable habits that could be easily dispensed because they lacked instrumentality. They were ways of organizing people that had served the company well during its rapid rise to prominence within the diagnostics industry. Lilly's efforts significantly improved

---

bit, too: "The mobile signifies two things to me: Balance and Constant Change. Balance means that all parts are consistently in harmony working in perfect harmony, a goal we should always strive for as a successful company. Change signifies that a mobile is in constant motion, responding sensitively to a consistently changing and evolving environment. Again, any successful company must be similarly responsive, but this is particularly true in our business. Finally, change and response to change must take place even if transiently upsetting the balance between components." The last two sentences can perhaps be read as a complaint about the sluggishness of the 'Lilly way,' in which order and the maintenance of administrative control took precedence over innovation.

[30] "Q Corner: HTE Training Now Company-Wide," The Magic Bulletin, April 1989, iv, 3, p. 5. TQA stands for 'The Quality Advantage.'

Hybritech's COPS figures, but, David says, "I think they did a lot of damage by forcing us to push it down as far as we did." Cole Owen elaborates:

> Lilly made some changes, some that needed to be made – they brought in a much more routinized process for manufacturing, quality control, things that were very appropriate. It was really beneficial to Hybritech to have that expertise come in, but Lilly also brought in some thought processes and assessment processes, and background from which judgments and management decisions were made, that were not consistent with the new business that it bought into. A lot of people sort of threw up their hands and said, 'I can't do it this way.' That was sort of predictable. It's not a negative for Lilly, it's a reality. It's what they have to do, but a lot of times, it gets overdone, and you end up damaging what you acquired.

Lilly, perhaps without fully understanding the implications of its actions, altered the manner in which Hybritech's performance and progress were measured.[31] The Lilly regime imported its own objectives, definitions of success, and criteria for evaluating the company's efforts. Hybritech's strategy from the beginning had been to make a place for itself by innovating, by inventing and creating. The principal goals of the company, endorsed by its board of directors, had been to introduce new products rapidly and build market share in the immunodiagnostics business. Efficiency in production had been deliberately sacrificed in order to accomplish these ends, and the technical advantages afforded by hybridoma technology and monoclonal antibodies had enabled the company to remain competitive while doing so. When Lilly came along, however, it changed the ground rules. Under the Lilly regime, profitability was to be the key measure employed to gauge success. Hybritech's performance during in its first seven or eight years had, according to this criterion, been only marginally acceptable. The company's high COPS numbers and its meager

returns on massive R&D expenditures appeared to be symptoms of grossly inefficient uses of scarce resources. Lilly apparently intended to correct this operating 'deficiency.' This didn't prevent Grimm and others in the organization from paying lip service to the goal of innovation. A headline over one of Grimm's "President's Message" columns in The Magic Bulletin asserted that "Scientific Innovation is Key to Our Future." But qualifications in the article text betray Lilly's prejudices on the matter: "Innovation in the management of science," Grimm stated, "will be just as important in the future as scientific innovation itself."[32] According to David Kabakoff, when Lilly came in and instituted its approach to doing business:

> The emphasis shifted from expansion of the organization and rapid introduction of new products, with the attendant problems that that would bring, to the profitability of the business, not that that was a bad thing, but my own experience is it takes longer than Lilly allowed, or was willing to try to allow, to convert the mind set and values and measurement tools for an organization. You just can't do that overnight. The people were accustomed to making decisions based on what can we do to get this product to market sooner. By definition, it meant that you didn't spend the months of process development to see if you produce it at a lower cost, because getting to market sooner was the priority. Now, all of a sudden you start changing some very fundamental ways that an organization works, product improvement, maintenance, cost reduction, all those things started becoming much more important than new product introduction.

Lilly made the changes and the organization felt the effects. Before Lilly, Hybritech had been in the business of making innovations. After the acquisition, Hybritech began making products better, but it stopped making better products. The project of maximizing efficiency in production is antithetical to the project of making

---

[31] Don Grimm declined a request for an interview, so his side of the story can't be presented here.

[32] Don Grimm, "President's Message: Scientific Innovation is Key to Our Future," The Magic Bulletin, September 1989, IV, 7: 3.

innovations. Efficiency maximization requires control. Control requires stability. Stability comes with regularity, and, by definition, disappears with change. Change is disruptive. If a manufacturing operation is set up to run optimally with given sets of materials and processes in a stable, regular way, then introductions of new materials or processes are necessarily destabilizing, irregular, and inefficient. And the more fundamental the change, the greater the departure from the established order or system, the more revolutionary the innovation, then the more substantial are the costs of organizational adaptation. In the mid-1980s, hybridoma technology and monoclonal antibodies were still new and people were just figuring out what could be done with them. Asking Hybritech to hold up new products until fully scalable, cost-controlled production systems could be engineered was, in effect, asking the company to stop making innovations. There are compromises to be made and bargains to be struck between complete administrative control and complete innovative freedom, and Hybritech had wrestled with the issue before, but Lilly was earnestly committed to profitability and 'quality.' Hybritech paid the price. It stopped introducing new products, and its technological lead in the diagnostics industry evaporated. "There was a four to five year gap," says Kabakoff, "I mean, honest to God, a four to five year gap. In that industry, it absolutely killed them." David Hale sums up the lesson: "Big companies in general don't develop products well."

Bill Crean offers an alternative view of the episode. He maintains that Don Grimm's quality programs and his process engineering efforts represented attempts, not just to cut costs and promote the Lilly orthodoxy, but also to boost morale in a newly acquired subsidiary that was experiencing an identity crisis. In Crean's

opinion, Grimm was trying to defuse internal tensions that the acquisition and the Lilly 'invasion' had created within the firm. The employees spent a lot of time discussing the relative merits of the new 'Lilly way' and the old 'Hybritech way.' There were divisions between the Lilly people and the Hybritech people, and competition. There were sectarian debates about who had attracted and bred the better, more talented scientists, technicians, and managers – Hybritech or Lilly? The Hybritech folk felt a fair amount of indignation when Lilly came in and told them how to take care of business. Their collective reaction was 'We've been doing just fine, thank you.' In this environment, Grimm wanted people to stop fighting and start working together. He wanted them to do good work and put good products on the market. His message, as Crean puts it, was "'Let's focus on the customer, let's refocus on the science, and let's focus on being successful again.'"[33] Crean developed a close relationship with Grimm, and defends his friend against charges that he damaged the company. He believes that Grimm was a good choice to lead Hybritech:

> Don was sort of liberal, out on the fringes of Eli Lilly, in terms of his thinking and his leadership. I think they were wise to go to someone like that, because Don could understand the Hybritech approach and culture, and then try to help facilitate where that acquisition was and where it needed to go. I heard from different people that I worked with that Don was always a – renegade is too strong a word – he was in the Lilly mold somewhat, but he was a fairly independent thinker and was not afraid to voice his independence in a way that Lilly could live with. Some Hybritech people would do that and sort of talk themselves right off the table. The Lilly people just didn't understand them, or they didn't have the credibility that Don had.

[33] It's not clear, however, that 'focus on the customer' (i.e., 'quality' standards) and 'refocus on the science,' given the way Grimm employed the terms, were coherent ends.

If Crean is right about his boss's status and reputation within Lilly, then Grimm's dilemmas, his programs, and the decline of the company under his direction all further underscore the incompatibility of the 'Lilly way' and the 'Hybritech way.' Many Hybritech folk have questioned why Lilly ever bought a small, R&D powered biotech firm if it intended to reconstruct it – or smother it, if necessary – in order to ensure that it didn't waste any money. Lilly had already initiated its own purely experimental monoclonal antibody research program. It certainly didn't require any particular COPS figures to justify the maintenance of that wing of its in-house R&D operation – its monoclonal division wasn't selling anything. Did Lilly purchase Hybritech for its know-how or its profit margins? Some have concluded that the old pharmaceutical corporation simply didn't understand the diagnostics business. Tina Nova, from her place in the trenches, observed: "They weren't diagnostics people, they were therapeutics people. I think that Eli Lilly bought a diagnostics company, and they thought they had bought a therapeutics company." Development times in the pharmaceutical industry are elongated. As the industry is presently organized, it takes, on average, a dozen years to carry a new drug candidate through product development, clinical testing, and regulatory approval processes. The diagnostics business, in contrast, moves much faster. Process engineering is important, of course, but in relative terms, less so than in pharmaceuticals. At the same time, capacities to make rapid innovations are almost always fostered in diagnostics, if they can be, because they so often afford crucial competitive advantages; executive bodies are probably ill advised to bridle them for the sake of cost reductions, except perhaps in dire

circumstances. This is especially true for small companies in the field. Hybritech's diagnostics business wasn't well served by Lilly's impatience over its profit margins.

DISENCHANTMENT AND CHARISMA

After the sale, most members of Hybritech's upper management team had planned to stay with the company, initially, at least, for the three-year transitional period. Cole Owen was the first to exit after the merger. He didn't sign an employment agreement. Owen had been involved in acquisitions before, when he was at Johnson & Johnson. He had an inkling of what was about to occur: "I knew that I would end up sending the goldenrod copy to Indianapolis to ask them if it was OK for me to do something that I'd been doing for the last five years, so I just said, 'I'm not going to stay.'" Some of the others believed that the employment contracts represented good faith pledges to let Hybritech's management run the company as they had been – successfully. Ron Taylor now holds an alternative and more caustic view. "They didn't want us all leaving the next day," he says. "They wanted us hanging around, but they knew that we hadn't come to Hybritech to collect Lilly pensions. So, they wanted to sort of lock us up with some kind of golden handcuffs. What they really wanted to do was manage our departure over a period of time." When Lilly moved in and started to redecorate, Hybritech's senior management began departing, one by one. They each left separately, but they all went for the same reason – they realized that they wouldn't be happy in the employ of Eli Lilly.

David Kabakoff stayed at Hybritech until the spring of 1989, running the in vitro diagnostics division, so he was around to watch the company absorb the full dose of Lilly's organizational therapy. He had previously enjoyed a great deal of freedom

and autonomy in doing his job, but, at the first opportunity, he says, Lilly imposed several additional levels of administrative oversight and control. Kabakoff wasn't pleased with the restrictions. Decisions that he had previously made independently and routinely, as a matter of course, were suddenly subject to review locally and by Indianapolis. It was all to no productive purpose as far as he could tell: "You know, I just said, 'Hey, this is crazy.' All the fun kind of went out of it." Kabakoff is puzzled about why Lilly felt they had to regulate the workings of the organization to the extent that they did, and why he wasn't allowed to run diagnostics in the unencumbered manner he had before the merger. His guess is that it was just a matter of cultural conditioning: "You just couldn't give one individual or one group that much control over a piece of the business and their own destiny. That was, like, against the culture. There was no way you do that."

Kabakoff became increasingly disenchanted after all of his compatriots had gone. "The last year at Hybritech," he says, "wasn't a lot of fun. I had complaints, and voiced them about how I was treated in terms of my ability to do my job." The straw that prompted him, finally, in 1989, to look around for different work, had to do with a hiring decision. When Tim Wollaeger was dismissed as the firm's CFO, Lilly called up a replacement from within its own ranks. The new man stayed on for two years, but was later transferred to a different division within the corporation. Another substitute was picked, but Kabakoff wasn't included in the selection process. He felt that Hybritech had a good internal candidate for the position, and he thought that, as vice-president of the diagnostics division, he should have been consulted about the appointment:

> I remember a discussion, both with my boss, and one of the HR guys, "Gee, you know, we have a guy, David Duncan, who is a controller of this company, and the guy's probably ready, he should have gotten that job, or at least be considered,' OK? Here I am, I'm a senior vice-president of this company, and I have nothing to say? There's no process, no discussion whereby we talk about filling a key job like, you know, VP of finance of this company? And the answer from some career HR guy was, 'At Lilly, you'll be consulted when you've earned the right to be consulted.' And I just said, you know, 'That's an insult, sir. I mean, this is ridiculous. I'm an executive of this company. I've been running this company for a long time. I've earned that right, OK? Don't talk to me like that.' I mean, it was just insulting. It was demeaning. And you know, it was countless things like that. I said, 'Fine, you guys, you know, good luck to you.'

The Hybritech upper management group left because, after Lilly took over, it wasn't their company anymore. The scientists at the firm also chafed at the control exerted by Lilly. Bill Crean, who kept tabs on such things in human resources, reports that, after the acquisition, the turnover rate reached 18%, an usually high figure: "Lilly was wondering why people were leaving and they were especially worried about the scientists, because I think they made their investment on the monoclonal antibody technology, and if the science people leave, that technology floats out with them." Hybritech suffered from a brain drain under the Lilly regime. The scientists tell stories about why this occurred. Previously, they had enjoyed a great deal of autonomy in the laboratories. Tina Nova says, "The neat thing about Hybritech is that there was a lot of freedom. You could really do what you needed to do, and you didn't really have to get approvals every time you wanted to do something. Once they trusted you to do something, you got to do it. They'd say, 'That's you're job, go do it.'" Hybritech hired Nova in 1983, to work on assay chemistries in diagnostics. "It turned out," she says, "that I was given the worst project in the whole company, but I

didn't know that at the time. They asked me to work on the stabilization of prostate specific antigen, PSA, in serum." The instability of the protein had been holding back the development process for over two years. Nova put her blinders on:

> I sat there by myself and worked on this PSA stability problem. I really didn't talk to anybody for two months. And then, we had a project review. I said, 'Oh, I've got this figured out.' And they said, 'You what?' I said, 'Well, I've got this figured out.' And they said, 'You've got to be kidding. We've been trying to do this for years.' And I said, 'No, it's really quite simple.' So, that was quite exciting.

Nova was then instructed to explain to the appropriate persons what she had done so that the invention could be patented:

> I didn't even know what patents were or what they meant. I sat down with Larry Respess, who was the general counsel at that time, for hour after hour after hour, explaining to him this invention, how I came up with it, and what sorts of things I thought you could do with it. And I just thought, 'You know this is such a waste of time, sitting here going over this.' And now, I look back, and I think, 'Boy, was I stupid.'[34]

The PSA test became Hybritech's biggest cash cow. It was, by far, the most profitable TANDEM kit that the company ever marketed. It was a high-priced test and it constituted a revolutionary breakthrough in medical diagnostics. The PSA kit is a product that many Hybritech folk still take pride in. They like to think about how many early stage tumors the assay has detected.[35] Tina Nova made a name for herself

---

[34] Tina S. Berger [Nova] and Linda P. Ivor, "Processes for the stabilization of prostate specific antigen in natural matrices," U.S. Patent No. 5,242,802; filed March 29, 1985; issued September 7, 1993.

[35] The TANDEM PSA test revolutionized prostate cancer screening. Prostate cancer rarely produces symptoms before it has metastasized. Prior to the introduction of the Hybritech assay, digital rectal exams were the only means of detecting the condition. Hybritech's invention vastly increased physicians' capacities to diagnose the disease in very early stages. However, while prostate cancer is a leading cause of death in men, it is often indolent, i.e., very slow to advance or spread. Treatments can cause impotence and incontinence, and aggressive forms of the disease remain difficult to distinguish from less lethal varieties. For these reasons, in addition to improving diagnostic capabilities, Hybritech's test introduced treatment dilemmas for physicians and patients. The medical profession is still engaged in debates about how to make determinations regarding the efficacy and costs of various

with the deft bit of chemistry she put into the kit, and she was having fun. She couldn't wait to go to work every day. As a reward for her fine contributions to the PSA effort, David Kabakoff put Nova on the CK-MB II project. CK-MB is an enzyme, another protein with stability issues. It turned out to be, she recalls, "a manufacturing nightmare." The work was difficult and sometime frustrating, but Nova liked it anyway. It was challenging. And she especially liked the fact that she was allowed to do it without interference, without surveillance, and without filing reports and filling out requisition forms in triplicate.

All of this changed when Lilly arrived on the scene, and Nova, along with many of her colleagues, was enrolled in reeducation programs: "I spent a lot of time in Indianapolis those last couple of years that I was there, and I found that the emphasis wasn't on the science. It was different. It was on management." The young scientist was mildly amused by what she saw, but also discouraged: "They wanted us to walk around with these buttons that said, 'I graduated from this quality program.' I'd gone into science to be a scientist, not to join quality teams. I started getting disillusioned." Nova had earned a Ph.D. in biochemistry at UC-Riverside, and had then conducted postdoctoral research at the NYU medical school. Her pay didn't go up when she moved to Hybritech. Her starting salary was a modest $28,000 per year. She hadn't joined Hybritech in order to get rich, so when the satisfaction that she derived from the work started to evaporate, she was ready to leave the job behind. She doesn't harbor any ill-will toward Lilly, she doesn't feel as if she was mistreated, and she considers

---

therapy options. See Marc B. Garnick, "The Dilemmas of Prostate Cancer," Scientific American, April 1994; and Gina Kolata, "Dilemma on Prostate Cancer Treatment Splits Experts," New York Times, September 17, 2002.

the experience valuable, but she realized that she didn't want to live in the big corporation. She decided that she would start looking for employment elsewhere:

> I got to go through the management training program, and go to the executive dining room, where the CEO from Lilly comes out, this perfect man, you know, with the gray suit, the gray hair, and the shiny shoes. If you drew a CEO, this is the guy you would draw. He came out and gave us our little certificates and what have you, and to see that, to be exposed to that, was really great, I mean, it really was. But, on the other hand, at that point, I sort of decided that it wasn't for me.

The introduction to Lilly's practice of big science was a rude awakening for many young researchers who had become accustomed to Hybritech's relatively loose approach. Some of them didn't accept the new Lilly regime with the good humor that Nova displayed. Very few appreciated Lilly's emphasis on process reengineering, and some felt ignored or neglected when the company didn't prioritize their particular projects or areas of expertise when budgets or allocations of personnel and labor power were decided. This was perhaps especially true in the diagnostics division. Lilly's primary focus was on imaging and therapeutics. Many on the other side were dissatisfied with the levels of support that they received for their programs after the acquisition, and rankled by what they considered Lilly's mismanagement of the diagnostics business. In March 1988, a group of talented scientists from the diagnostics division caused a huge stir in the company when, having become thoroughly disenchanted with the Lilly philosophy, they decided to pack up their laboratory utensils and leave together. The group was widely recognized as among the very best that Hybritech had. So, Crean reports, the defection "alarmed everybody."

In the winter of 1984, Gunars Valkirs, a young biophysicist, a new Ph.D. from UC-San Diego, had interviewed and was hired at Hybritech. Valkirs was assigned to a project called TANDEM improvement. He began investigating methods for increasing the speed and sensitivity of Hybritech's chemistries. In the TANDEM 'bead in a tube' formats, many of the molecules in solution had to travel long distances to reach the surface of the bead; in fact, it took them an hour or more to do so. "Working on those products," says Valkirs, "led me to consider the physical parameters that cause immunoassays to work as they do. I came across the idea that perhaps the solid phase shouldn't be a bead – perhaps it should be a membrane, perhaps the sample should flow through it, because the reaction kinetics are most favorable if you configure it that way." He did a few calculations, determined that it could work, and then began to experiment. One day, Cole Owen, then director of marketing, was walking through Hybritech's development labs and came across Valkirs sitting on the floor with a hammer and a two-by-four, banging away on a piece of gauze: "I said, 'Gunars, what the hell are you doing?'" The young biophysicist explained that he was working on a filtration-based assay that would be much faster than Hybritech's present products.

Valkirs showed Owen his plan for a visual HCG test that would work in under five minutes without sacrificing sensitivity.[36] HCG (human chorionic gonadatropin) is

[36] Hybritech was selling several different TANDEM 'bead-in-a-tube' pregnancy test kits. In these, the antibodies fastened to the bead react with a specific epitope, or binding site, on HCG molecules. To conduct the test, monoclonals that react with HCG are labeled with radioisotopes or fluorescing enzymes are poured into the tube along with a urine sample. If HCG is present in the sample, it reacts with both the labeled and unlabeled antibodies, and forms "sandwiches" that become fixed to the solid phase. The bead is removed and washed, emissions from the attached radioisotopic or enzymatic labels are measured, and from these measurements, HCG levels are calculated. Hybritech was marketing both radioisotopic and enzymatic pregnancy tests, and also had a third variant, an assay that could read be

a hormone produced by the placenta; elevated levels of HCG in urine indicate pregnancy. Owen, who had come to Hybritech from Johnson & Johnson, recognized immediately what the company had on its hands: "At J&J, I ran the product group that introduced the first immunologic pregnancy test. Before that, it had been frogs and rabbits, so I knew that market really, really well. I almost jumped out of my skin when I saw what Gunars was doing." Owen called some friends at Celanese Corporation, where he had once worked as an engineer, to secure materials with which Valkirs could experiment. Valkirs concocted a prototype comprised of a 12" x 75" test tube with the bottom cut out of it, cigarette filter material jammed inside to act as an absorbent, a porous synthetic membrane coated with monoclonal antibodies stretched across the top, and a small pump to flush samples through it. "I tried it and it worked the first time," says Valkirs, "and you know, it's fairly astounding, after having worked with assays that took an hour, to see a color develop in five minutes. Everybody was working on making twenty or thirty percent improvements in products, and all of a sudden, here was a factor of ten."[37] Valkirs had invented what came to be known as 'ICON' (immunoconcentration) technology.

---

visually. In this format, the binding of enzyme-tagged complexes to antibodies on the solid phase in sufficient concentrations would cause the bead to change color, from white to blue. The visual test was simpler and marginally faster, but it gave a purely qualitative indication; the test was either positive or negative.

[37] Valkirs' design serves as the basis for most rapid pregnancy tests now available over-the-counter. See Gunars E. Valkirs and Richard Barton, "ImmunoConcentration – A new format for solid-phase Immunoassays," Clinical Chemistry 1985, 31, 9: 1427-1431. Valkirs, Owen, and Phil Levenson, Hybritech's director of engineering, are named as co-inventors on the ICON patent. See Gunars Valkirs, Coleman N. Owen, and Philip Levenson, "Method and Apparatus for Immunoassays," U.S. Patent No. 4,632,901, filed May 11, 1984; issued December 30, 1986. As the assignee with control of this intellectual property, Hybritech out-licensed rights to its use.

Valkirs went to see Tim Wollaeger. "I didn't recognize him when he came to see me," Wollaeger recalls, "he'd only been with the company a short time. He was a physicist. I don't know why we had him, but he came in, and he had this glass tube with a membrane on it and a pump. He told me that he'd been able to suspend these antibodies in the membrane and keep them alive, and then, by sucking the specimen through it, he could get a blue spot to develop in five minutes. I just thought immediately, 'Man, that's neat.'" Wollaeger alerted the senior management group. The idea was well received, but no immediate action was taken to put product development wheels in motion. No one at Hybritech doubted that the assay could be commercialized or that it would do very well in the existing marketplace, but it was difficult, at that moment, for the company to dedicate the human and material resources necessary to turn Valkirs' crude prototype into a marketable product. Says Owen: "There was so much going on. There were a lot of close alligators. We had to keep products on the market and keep them working. We couldn't just stop to work on ICON." For a brief period, the project languished, until David Hale suggested that Wollaeger, having had prior general management experience, might assemble and direct a product development team. Wollaeger remembers, "He said to me, 'Tim, you always like to stick your nose in everybody's business, why don't you go ahead with it.'" Wollaeger agreed. He claims no technical expertise, but says:

> This was something I could understand. You put a few drops of urine on it, and in five minutes it turns blue. It was magic, absolute magic. Instead of having a woman come into the doctor's office, take a bottle home, take first pass urine in the morning, bring it back, send it to a lab, get the results back, this thing was so sensitive that you didn't have to have first pass urine. The woman would come in, the receptionist would say, you know, 'tinkle on this thing,' and the doctor would say

> you're pregnant. You cut three days out of the process. So, Gunars Valkirs, Cole Owen, and I sat down to do this project.

Wollaeger organized a development team, and made sure that it would be able to procure the resources necessary to make a real product out of Valkirs' assay. He then proposed to Hale that Kim Blickenstaff, one of his assistants in finance, be allowed to take over the project. Wollaeger was Blickenstaff's mentor. Blickenstaff had worked for him at Baxter, had followed him to National Health Laboratories, and then had been recruited by Wollaeger to Hybritech. He was chomping at the bit to broaden his horizons, to gain marketing and general management experience. Hale gave him the assignment. To round out the development team, Blickenstaff borrowed two chemists, Ken Buechler and Rick Anderson, from other groups in the diagnostics division. Blickenstaff looked after the administrative and marketing aspects of the project while the scientists set out to polish the assay and package it into an easy-to-use kit. The work moved along rapidly, and the team soon had a format to present to David Kabakoff. Kabakoff, naturally, was pleased as punch. "This," says Blickenstaff, "was the Holy Grail."

Through the summer of 1984, Blickenstaff and the others worked closely with Bob Wang and Ron Taylor to organize the manufacturing of ICON kits. When Hybritech decided to proceed with ICON, it also elected to rush the product to market. David Hale had set a target date for the first shipments: October, less than six months after Valkirs had made his invention. "That was unheard of," says Valkirs, "trying to accomplish that." There would be no chance to do extensive planning or to install high-volume manufacturing techniques. ICON was to be assembled by hand, by

armies of people. The Hybritech strategy was to price the ICON high, in order to skim the top of the market. It was expected that when the product reached maturity, the company would be able to move 100,000 units per month. One million units were shipped in December of 1984. Blickenstaff remembers: "We priced it at a premium and still it took off like a rocket. Our sales people went nuts. We had made up probably fifty kits, one for each person at the launch meeting, and they grabbed these things like they were gold. They ran out to the phones at the break to call their accounts. You know, 'I've got a sales meeting, I'll get there as soon as I can, but wait till you see what I've got.' And the sales just took off." In 1985, the ICON pregnancy test accounted for one-third of Hybritech's sales. The development team basked in the glory. They earned a good deal of prestige and respect within the company for what they had accomplished.

After the merger, Valkirs and his collaborators found that Lilly didn't care about any of that. The new managers arrived from Indianapolis with their own agendas. They didn't know the history of the place, it was evident that they had no interest in learning about it, and it seemed to Valkirs that they weren't much more concerned with the work that was being conducted in the diagnostics division. "My perception," he says, "is they bought Hybritech for the therapeutics and the diagnostics came along for the ride. It was like 'Let's put these guys off in the corner and forget about them.' That's what it seemed like to me." Valkirs was annoyed that big chunks of the diagnostics R&D budget were dedicated to 'technical product support function.' Lilly was taking money from development, money for innovation, to pay for improvements in manufacturing. As Valkirs' saw it, "They perceived the

products in the field to be flawed and the process for manufacturing them to be flawed. They wanted to fix that. The kits weren't under the kind of control that a pharmaceutical product is, and they perceived that to be a problem." His frustration peaked in the summer of 1987. As Lilly siphoned resources in order to reduce Hybritech's COPS numbers, Valkirs found that the effort was also making the manufacturing department jittery and conservative. He was working on ICON improvements (the project was named ICON II) but found that he couldn't get any support from the people in operations – involvement in the production of a novel diagnostics kit would just cause them trouble on paper. It would make them look bad. Gunars used to be a hero around the place, but now, people were turning their backs on him: "I was trying to push through the new ICON format, which involved this latex deposition for the pregnancy test, and the internal reference. I was trying to push that through in the summer of '86, and I ran up against a stone wall. The stone wall was operations. They were afraid to fail."

The company was afraid, too, that the competition would figure out a way around the ICON patent. Valkirs' technology had enabled Hybritech to bound far ahead in the market for pregnancy tests, and the company was preparing to develop a fast test for strep, too. In all likelihood, others in the diagnostics field, including powers like Abbott and Roche, had already begun organizing efforts to reel the San Diegans back in. Hybritech wanted to prevent that if it could. After Lilly's appearance, Rick Anderson, one of the ICON chemists, had been splitting his time between ICON II development and manufacturing, which was experiencing problems with the first ICON. His boss, Ian Wells, came to him, in the summer of 1987, and

told him that his new job would be to work with Valkirs to defeat the ICON patent, to produce a five-minute immunoconcentration assay without infringing on Hybritech's intellectual property. Anderson remembers:

> I was supposed to try to get with Gunars and try to figure out how to break the ICON patent. And I thought that that was kind of an interesting concept, kind of funny, actually. I ended up stopping Gunars one day in a hallway, and saying, 'Oh, Ian says that we're supposed to do this,' and I sort of made a half-joke and said, 'Well, if I knew how to do that, I don't think I'd want to do it here.' And Gunars was apparently listening to what I said, so he came back later and asked me whether I was serious, and I said, 'Serious? About what?' And he said, 'Serious about if you knew how to do that, you wouldn't want to do it here?' I said, 'Well, yeah.'

Blickenstaff, who Lilly had placed temporarily in sales, recalls seeing Valkirs and having a similar conversation: "I ran into Gunars, and I hadn't seen him in a long time, and I said, 'Gunars, how are you doing? Is Lilly getting to you yet?' And he basically looked at me, and I think he said something to the effect, 'You know, I hate this fucking place.' I said, 'You want to get out of here?' And he said, 'I'd love to.' Wheels were turning all around. Some time later, toward the end of 1987, Blickenstaff received a phone message from Valkirs.

> Gunars and I never got together. We never socialized, we never got together for lunch, but I got this voice mail, so I called him back, and I asked, "What is this all about?' And he said, 'Well, I'd rather just talk to you at lunch.' So we had lunch at a Chinese restaurant over by UTC, and Rick Anderson, Ken Buechler, and Gunars Valkirs show up, and they basically said, 'Look, we're getting out of Hybritech.'"

They had something else in mind, and they wanted Blickenstaff to join them. He did. Gary David says: "That's a sign that something isn't quite right with a company, to let a group like that get away." Morale among the scientists was sagging. Jackie Johnson, Hybritech's chief molecular biologist says it began with the defection

of the ICON team: "People started to leave. They were some of the core researchers in diagnostics, Gunars and Ken Buechler. People just started peeling out of there." Something special was escaping the corporation.

SHUTTING DOWN

Some who observed Hybritech's decline in the late 1980s believe that Eli Lilly mismanaged the company's imaging and therapeutics programs, as well as diagnostics R&D. By the time of the merger, Lilly had already acquired its own stable of monoclonal specialists. Its researchers were good, by all accounts,[38] although Hybritech's program was the more technically advanced. Hybritech had gotten out of the gate ahead of everyone in 1978, but there was also more at stake for the San Diego group. Of hybridoma technology, Gary David says, "It was a tool to them, and it was a life to us, so you'd have to expect some differences there." There was some natural wariness and competition between the two groups that inhibited cooperation a bit, but also some differences when it came to product development strategies. Lilly was hoping to use monoclonal antibodies as delivery vehicles for the corporation's cancer cocktails, chemotherapeutic agents that physicians were already putting into patients by methods featuring much less precision. Hybritech's immunochemists didn't like that idea. They preferred radiation therapy because side effects could be significantly reduced, and because attaching bulky chemical compounds to antibodies would almost

[38] By all accounts, that is, except Sam Halpern's. Halpern contends that Lilly's misguided ideas about monoclonal antibodies ruined Hybritech's in vivo R&D. "In my opinion," he says, "Eli Lilly destroyed it. I will believe that till the day I die, and I don't care what they think about it. You can write that if you want to because, in my opinion, they did not know what they were doing. They had preconceived opinions of what antibodies were all about, what you could do with them, what you couldn't do with them." When Lilly purchased Hybritech it shut down most of the smaller firm's collaborative research projects, including the work conducted at UCSD with Halpern.

surely alter their pharmacokinetic properties in unpredictable ways – an undesirable result when the payloads are toxic. Gary David explains:

> A drug kills a cell by getting into the cell. A radioisotope kills a cell like a bullet. It was pretty obvious to us that the drug route was a nasty route. And there were other pieces of it, like immunogenicity and chemistry, and denaturation, what you're doing when you conjugate big molecules, and usually hydrophobic molecules, antibodies. It made no sense. So we had some philosophical differences on approaches to use.

It seems that differences between the monoclonal researchers at Hybritech and Lilly extended beyond technical issues to organizational matters, as well, to styles of scientific practice. Sam Halpern suggests that, just as happened in other areas of the company, Hybritech's in vivo R&D teams had to adapt to Lilly's favored methods of conducting business and conducting research. His former associates complained about losing the freedom to plan and conduct investigations, without (what they perceived as) a pointless and redundant series of administrative clearances and approvals. "What Lilly did," Halpern asserts, "was stop the intellectual ferment. Everything became the Lilly way. I used to hear those guys comment about it, they would say, 'Why don't we do things like Hybritech used to do things? Let's do it the old Hybritech way.' And of course, they could only do that so much before they got in trouble."

Hybritech's scientists also felt that, following the departure of Dennis Carlo, vice-president of in vivo R&D, early in 1987, the program lacked a coherent sense of direction. The research, it seemed, started branching chaotically, in fits and starts, and in numerous directions simultaneously. Jackie Johnson was at the head of Hybritech's molecular biology group. She says, "We had a lot of different bosses, and there wasn't a good clinical focus. What you see in the clinic should be feeding back to

research, but, at that point, it got kind of crazy. There was a complete disconnect between research and the clinic at Hybritech, in therapeutics." Gary David blames the confusion on mixed signals coming from Indianapolis: "Their support went up and down, and part of the problem was it was half-hearted for a while, and then it was intense for a while, then it was half-hearted, and it did not make for a stable environment." He adds that Indianapolis vacillated on where the Hybritech program should be devoting the lion's share of its resources and energies. The home office couldn't decide whether it wanted first to pursue imaging or therapeutics:

> Their initial interest was in imaging, and they discouraged us from putting a lot of energy into therapy. So, we shifted most of our emphasis away from therapy and into imaging. And then, they started questioning whether there was enough of a market, so we switched our emphasis back to therapy, and sort of put the imaging product on the backburner. And then, somebody ran some more numbers later on, and said, 'Oh, by the way, there is a good market in imaging. Let's go ahead and do that.' So, we went back to imaging.

The results were devastating – just as the diagnostics division lost its leading technological position among its competitors, so did imaging and therapeutics. Eli Lilly purchased Hybritech in 1986. At that time, both companies were optimistic that a useful, marketable imaging antibody could be developed within the next several years. By 1990, however, there was still no product. The indecision, false starts, and interruptions had slowed Hybritech and permitted others to catch up. The company had been working on an indium-labeled anti-CEA antibody, called HybriCEAker, for imaging colon cancer, and, midway through the year, it was ready to be submitted for review by the FDA.[39] But Hybritech was no longer in front of the pack. It wasn't the

[39] Nilda Weglarz, "Hybritech Seeks FDA Clearance for Colon Cancer Diagnostic Test," San Diego Union, August 9, 1990, p. E-1.

first commercial developer to manufacture an imaging antibody. Cytogen Corp., located in Princeton, New Jersey, had also produced an indium-labeled monoclonal, called Ontoscint, for detecting colon and ovarian cancers, and had filed with the FDA nine months before. For Gary David, it was a frustrating time. In July 1990, he wrote to his co-workers in The Magic Bulletin:

> Every year we worked hard to figure out how we needed to expand our basic technology into new areas. Every year we repeated the process. We did have some good technology, and we did need to expand it into new areas. But.... We forgot to figure in how technology in the outside world would catch up with us. We discovered that we no longer necessarily had the edge. That was painful. I know – I lived through it![40]

The company fairly botched the clinical trials for HybriCEAker, so approval of the antibody was held up for an extended period. By the summer of 1993, it appeared that it would finally be cleared for release. It also appeared that there might still be a market for it. Cytogen hadn't managed effectively to sell and distribute Ontoscint. It was a good product, in David's estimation, but it had failed to penetrate the market. Hybritech felt that it might be able to do better since it had Lilly's powerful marketing machinery behind it. Lilly had invested millions in a special facility in San Diego (called e-bay) for the production of injectable antibodies, and pilot production of HybriCEAker had commenced, but some financial analyses convinced the top brass that continuing with the project wouldn't be worth the effort. The big corporation didn't foresee enough profit in it. David recalls: "Folks back home started looking at numbers, and thinking about what we'd have to charge in order to get the kind of

[40] Gary David, "2020: A Clear Vision of Our Future," The Magic Bulletin, July 1990, V, 7: 4.

COPS that Lilly was satisfied with, and they decided it wasn't a product." At that point, David recognized that:

> The market window had really passed us by. Had we been able to get it out early on, had we just continued on our original program and been able to put the product out, it would have been fine. As it turned out, by the time the product was submitted to the FDA, and approved by the FDA, the program was closed down.

In October 1993, Lilly announced that it intended to terminate Hybritech's in vivo R&D program. Don Grimm released a statement to the press: "We are no longer able to justify the continued financial investment in our cancer therapeutic efforts. Without a commitment to therapeutic research, a continued investment in imaging, particularly the investment to create the infrastructure necessary to build an imaging business, cannot be sustained."[41] Karen Klause, president of the in vivo division, received a call from the FDA asking the company to reconsider pulling the product. "They liked it," she says. "They wanted to be associated with a good product that had been approved and that worked, but unfortunately, the decision had been made, so the whole thing died on the shelf." Many of Hybritech's researchers were bitterly disappointed. They believed that the product would have saved lives. The company indicated that its diagnostics division, the heart of the business, the part that generated the revenues, would continue. It wasn't mentioned that Lilly had closed the in vivo division so that it could clear the company's books before putting it up for sale. Abbott had been stealing market share from Hybritech in both pregnancy and prostate cancer testing, the firm's two most profitable niches, and there were no new product

[41] Craig D. Rose, "Lilly Downsizing Will Tighten Biotech Belt at Hybritech; 150 Employees Expected to Lose Jobs by Year's End," San Diego Union-Tribune, October 12, 1993, p. C1. Lilly offered to place all affected employees in new jobs either within the corporation or with one of its subsidiaries.

innovations in the pipeline. The cupboard was bare. In January 1994, Lilly admitted publicly that it planned to divest itself of Hybritech.[42]

For many reasons, Lilly's attempts to integrate Hybritech and to synthesize a new corporate culture hadn't worked out. The company never achieved the kind of performance that Lilly had hoped for, and when the parent corporation eventually lost interest, Hybritech became a neglected outpost at the edge of the world, about as far as one could get from Indianapolis. The company's pharmaceutical development program never came close to developing a product. In 1993, Lilly estimated that a therapeutic monoclonal antibody would probably have required another ten years of research.[43] The corporation decided not to wait on it. Gary David agreed with that decision. He had come to understand what small biotechnologies were up against in fights against diseases like cancer. He says, "Therapeutics is always a long ways away, further than anybody wants to realize." In fact, by the time Eli Lilly and Company shelved Hybritech's in vivo research, he had become convinced that the whole idea of using monoclonal antibodies as drugs or delivery systems was probably misguided. "There will be applications," he says. "There will be products here and there that will be very useful, but I don't think the antibody is the ideal, ultimate tool. It doesn't afford the control." The trouble with antibodies, in David's view, is that they're too big and too active in complex biological systems: "You don't want to wed yourself to the pharmacokinetics of an antibody. That's the tail wagging the dog." He

---

[42] Craig D. Rose, "3 S.D. Firms Included in Lilly Divestiture Plan," San Diego Union-Tribune, January 19, 1994, p. C-1.

[43] Craig D. Rose, "Magic Bullet That Missed: Hybritech Did a Lot Right, But Lilly Pulls Plug on New Drugs," San Diego Union-Tribune, October 26, 1993, p. C-1.

considers Hybritech's antibody research in therapeutics to have been educational but, in the end, never more than exploratory – never did it become a genuine product development effort.[44] As one might expect from a good biochemist, David now believes that medical progress will be realized through the modeling of proteins, their interactions, and their folding and conformation properties. He is placing bets on 'rational,' structure-based methods of designing therapeutic molecules. After an excursion through cell biology, David is back again where he started, in a sense, back in Al Nisonoff's lab as an undergraduate at the University of Illinois:

> The conclusion that I reached somewhere in the middle of all this is that, especially for in vivo use, the greatest value of an antibody is its training value. It taught us a lot. It taught us a lot about antibodies, it taught us a lot about delivery systems, it taught us a lot about using proteins in the human system in a serious way. It taught us a lot, from the modeling perspective, it taught us a lot about antibody structure and antibody-antigen interaction, and it still has a way to go, but I think this is the sort of learning process that ultimately is going to lead to optimizing a lot of pharmaceuticals. I think we stopped learning far too early. We're still learning, we're not focusing on learning like we were back in the days when we were actually modeling antibodies, modeling antigens, and modeling interactions.

Gary David stayed at Hybritech for a long time. Lilly had given him his own laboratory and let him conduct antibody research as he would, so he had been very happy with that. His project was named 'Blue Skies.' When the in vivo side of the operation was shut down, however, there was then no more exciting science left to do at Hybritech, and it was time for him to go. He had learned that science as a business is great when you're winning, but that it can be miserable when you lose. David

[44] David says, "I think that one of the most valuable parts of an antibody is its ability to teach about biology, about biology at all levels. It's turning out to be a model of what is happening in the CNS [central nervous system]. It's interesting, very interesting. I'm very into it."

regrets that Hybritech lost its edge and its momentum. He still contends that the old 'Hybritech way' was better: "The Hybritech goals, in a sense, were pretty good – 'We're ahead of the field, so let's give away some secrets, and by the time they catch up, we'll be in another dimension, anyway.' That's a wonderful attitude, and a very strong innovative attitude." Unfortunately, the company wasn't able to sustain this confident outlook after it grew large and was purchased by Eli Lilly. Following the merger, its spirit and value slowly dissipated. Perhaps Eli Lilly was to blame, but Hybritech had already started to change before the sale. Maybe the company had just gotten too big. In 1994, Lilly unloaded Hybritech to Beckman Instruments for a reported $10 million.[45] The acquisition had been a disaster.

THE BEGATTINGS OF HYBRITECH

On the evening of Tuesday, February 20, 1996, a large group of people gathered in the Mission Ball Room of San Diego's Bahia Hotel, for a special event. The affair was sponsored by Ernst & Young, LLP, Price Waterhouse, and Wells Fargo, among others. In attendance were the most prominent among San Diego's civic and business leaders. The first person rising to speak was Tom Creamer, formerly a senior vice-president in Shearson Lehman Brothers' San Diego office. He was acting as a special assistant to the president of the Greater San Diego Chamber of Commerce. Creamer introduced San Diego Mayor Susan Golding. Golding was followed by Louis T. Rosso, the chairman of Beckman Instruments, Inc., and then Steve Cushman, chairman of the Greater San Diego Chamber of Commerce. A thick

[45] "Lilly Gets Out of Biotechnology and Medical Diagnostics," Wall Street Journal, October 2, 1995, p. B4.

booklet had been passed out to invited guests. On the first page, was written: "This booklet has been created to commemorate an evening honoring the Founders and Officers of Hybritech, Incorporated and the institutions and individuals who have served as the cornerstones for building the biotechnology industry in San Diego – third largest in the world." Among the honorees were listed Tom Adams, Howard Birndorf, Brook Byers, Dennis Carlo, Cam Garner, Ted Greene, David Hale, David Kabakoff, Karen Klause, Tom Perkins, Larry Respess, Ivor Royston, Ron Taylor, and Tim Wollaeger.

It was a pretty big to-do for a company known lately around town mostly for its failure to live up to its potential and promises. Hybritech had recently garnered plenty of attention in the local press, but only for losing revenues and profits, scaling back production, and cutting jobs. Of course, the honorees weren't being blamed for any of this. They were being recognized for what they had accomplished at Hybritech before the company began its slide, and for what they had created in San Diego in the decade since Hybritech's acquisition by Eli Lilly. The organization itself, by 1996 a subsidiary of Beckman Instruments, was slowly dimming and cooling like a white dwarf, out on Terman Court, in Mira Mesa. The sponsors of the reception weren't much interested in Hybritech present. They were celebrating Hybritech past, and the luminous collection of biotech stars that the company had produced – the group that had gathered that evening like a galaxy of red giants in the Mission Ball Room. The members of the local elite were acknowledging what others (journalists, business analysts, social scientists, think tankers, etc.) coming from near and far to study San Diego's success in biotechnology would soon find out – that these individuals played

important roles in the formation of San Diego's proliferating cluster of young, dynamic biotech companies.[46] The brief histories of San Diego biotechnology that often precede accounts of the cluster, or this or that company, person, or group within it, in newspapers, magazines, business journals, or policy studies usually center on the stories of Ivor Royston, Howard Birndorf, and the vice-presidents of Hybritech, Inc. Here is an example, an excerpt from a study conducted by Harvard Business School professor Michael E. Porter on the sources of innovation in the cluster of new companies that comprise San Diego's biotechnology industry:

> An important event in the development of the cluster came with the founding of Hybritech in 1978 by UCSD scientists Ivor Royston and Howard Birndorf. Hybritech became the first nationally successful biotechnology firm in San Diego. It also became the training ground for the large number of scientists and managers who would later found more than 50 biotechnology or pharmaceutical companies in the region. Within two years of Hybritech's sale to Eli Lilly in 1986, alumni of the company founded at least eight new firms.[47]

On Porter's list of the "key events" that led to the creation of the San Diego cluster are:

- Salk decision to locate in region;
- formation of UCSD (and its ambitious research agenda);
- success of Hybritech (and sale to Lilly).

---

[46] Some would like to amend the celebratory stories that circulate about this group. Bob Wang, for example, whom Ron Taylor describes as "really cynical," comments on the guests of honor at the reception: "You know, they went on to do other things, and they can list on their resumes that they were integral parts of Hybritech and helped it to become successful, but no more so, and probably less so, than a lot of other people who were at levels below them, in my opinion. And people made a lot of mistakes. The vice-presidents, you know, their mistakes are much more obvious, but we waded through them."

[47] Michael E. Porter, Clusters of Innovation Initiative: San Diego, Washington, D.C.: Council on Competitiveness, 2001.

Porter also tells why Hybritech, in particular, was so important to the formation of the local industry and innovation in San Diego:

- it demonstrated to the local business and financial community that the industry was viable;
- it was an incubator for entrepreneurial biotechnology managers;
- its sale provided significant capital to employees eager to start new businesses.[48]

By the mid-1980s, a number of other biotech companies had gotten underway in San Diego – Agouron, Immunetech, Depotech, Molecular Biosystems, and Synbiotics, to name just a few – but Hybritech was first, and, for a long time, the most successful. When Hybritech was purchased by Eli Lilly, many persons at the company became wealthy. They could afford to seek out new opportunities, and they did. When these individuals left the firm, they remained in San Diego and began to start new biomedical companies in the area. Their associations with Hybritech had provided them with experience, connections, and 'an aura of success.' They had learned how to start and run biotech companies. They knew how to attract financial and technical resources from venture capitalists, universities, and scientists; they knew how to build out laboratories; they knew how to organize people and scientific projects; they know how to put together offices, departments, and teams; they knew how to manage finances in high-tech operations; they knew how to manufacture things (although not very well, apparently); and they knew how to handle regulatory affairs and intellectual properties.

---

[48] Michael E. Porter, Clusters of Innovation Initiative: San Diego, Washington, D.C.: Council on Competitiveness, 2001, p. 44.

They knew all sorts of things. They knew all about the world of biotechnology because they had, in a sense, invented it at Hybritech. Later, they applied their knowledge to build new biotech firms and spur the growth of the San Diego cluster. The group had already constructed an extensive web of social ties while working together at Hybritech. After leaving, they used links in the network as conduits of information and resource distribution. And they continued to expand and reinforce the network as they became 'serial entrepreneurs' and assisted each other in the founding and operation of more local companies.[49] What they produced, Birndorf says, is an environment in which "starting a company is like falling off a log."[50] The Hybritech group initially drew all of the necessary resources together. They showed how it could be done, and that got the ball rolling. Birndorf explains the appearance of San Diego's biotech industry in this way:

> I think the fact that there's venture capital, managerial talent, and entrepreneurial attitude here in San Diego, coupled with the fact that you have these major research institutions within three square miles supports the whole reason that this cluster is here.... The network is so in place, for not just money, but the facilities and the legal support, both corporate and patent, the lab supplies, you name it. Everything is here, easily available and even if somebody has no clue about what that is, there are so many people around here who do know now and can help somebody who wants to do it. You've got serial entrepreneurs – Hybritech for some reason spawned a dozen or two dozen serial entrepreneurs.[51]

---

[49] Members of this group still form an 'interlocking directorate' in the region – they sit together as directors on the boards of other's firms, and at others scattered throughout the San Diego industry, and in other places around California, as well, including the San Francisco Bay Area, Los Angeles, and Sacramento.

[50] Ross DeVol, Perry Wong, Junghoon Ki, Armen Bedroussian, and Rob Koepp, America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions, Santa Monica, CA: Milken Institute, 2004, p. 16.

[51] Ross DeVol, et al., America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions, p. 17.

The Hybritech group has been so prolific and so successful because of the personal relationships that they've established among themselves, and in the sciences and in the financial community. They're plugged into the sciences. They're aware of what's going on and what's new, and they've proven themselves to be astute evaluators of unproven technologies. And they learned at Hybritech how to raise money from the venture capitalists and from corporate partners, in order to make things happen, and now, because they know what they're doing, the money people have confidence in them. Because they've delivered in the past, they're able to go back and tap the same wells. The same venture syndicates fund their companies time and again. Of course, many others in San Diego have learned the same lessons in the past twenty years – and many directly from Hybritech folk. Cole Owen remarks: "We had made a lot of mistakes at Hybritech. I mean, we were doing a lot of things, in some cases, things that hadn't been done before. So, you could help people not to step in a lot of potholes, as well as show them which direction you thought would be most beneficial for them."

Today, Hybritech's legacy in San Diego includes impressive array of companies. The local industry's most successful firms, its highest flyers, have been started and run by ex-Hybritech personnel. As Porter suggests, it was Hybritech, as much as technologies that came out of UCSD, Scripps, or the Salk, that put San Diego biotechnology on the map. Estimates vary on the number of local biotech firms with ties to Hybritech. David Hale repeats what he has heard from people who count such things: "The most recent surveys indicate that over 70 companies were founded by the

senior management of Hybritech."[52] In any case, there are many, and the number continues to grow. Many of the principals were very young when the company began in 1978. Birndorf was only twenty-eight, Royston was thirty-two, and Ted Greene was thirty-six. Not a soul in the entire place was then over forty years of age. Most of these people are still in San Diego, and they're not finished just yet. In many ways – as founders, as executives, as board members, as venture capitalists, as 'angels,' as consultants, as mentors, etc. – the Hybritech folk are still contributing to the flowering of biotechnology in San Diego.[53]

---

[52] San Diego Regional Technology Alliance, San Diego Region Life Sciences Strategic Plan: Taking Action for Tomorrow, San Diego, CA: San Diego Regional Technology Alliance, 2003, p. 38.

[53] Of course, individuals who were positioned in lower levels of the organization are making important contributions, too. In its hey-day, Hybritech employed over a thousand people, and many of them can still be found today scattered among the newer companies that now populate the Sorrento Valley, Torrey Pines Mesa, and the other industrial precincts surrounding UCSD, Scripps, and the Salk. These are people with a lot of practical experience. Many started out in the labs and have now moved into management positions, and they, too, know how to get things done in biotech R&D. And others are now responsible for some of the 'peripheral' companies that provide support services to the biomedical community. Biostruct, for example, is a firm that specializes in laboratory construction. It was founded by Bruce Birch, who was Hybritech's facilities manager for fourteen years. He moved on to Gensia, for a time, where David Hale was the CEO, and then worked as a consultant in the area before starting the construction company. Biostruct vans are familiar sights on the streets around UCSD and the industrial parks that house many of the city's biotech companies. In 1988, Jeanne Dunham, Hybritech's first manufacturing person, started Bioserv, a contract manufacturer specializing in small runs of parenterals and medical devices. The company was financed entirely by Dunham's early Hybritech stock. She started small and has never raised additional capital. The company has been able to finance its own growth. Much of her business is based outside of San Diego, but among her list of customers can be found numerous local companies, and many with Hybritech connections. Mentus is an advertising agency founded by Guy Iannuzzi. Iannuzzi got his start working on marketing and advertising projects for Hybritech. Mentus now does annual reports, investor relations, public relations, marketing, and advertising work for a wide range of San Diego biomedical companies. Other Hybritech alumni have gone into different lines, but are still working on projects that will perhaps help to sustain the vitality of the biotech community into the future. Bob Wang, for example, and oddly enough, has become an academic again. After following Tom Adams to Gen-Probe and then to Genta, an antisense company that Adams founded, he and Dale Sevier are back together once more as faculty members at San Diego State University, in bioengineering and a regulatory affairs master's degree program. Walt Desmond, who stayed at Hybritech from 1979 through 1995, has a position in the San Diego public school system. He runs a bioscience magnet program that prepares high school students for study in the life science disciplines at the collegiate level. Hybritech is today defunct, but it continues to have an impact the local industry in innumerable ways.

The first Hybritech spin-off company, called Gen-Probe, came about after the organization had entered its period of exponential growth, and was no longer a suitable home for all of the innovative ideas and technologies that the firm's scientists were creating or learning about from others. Hybritech had been founded as a science-driven, scientist friendly company. Scientists joined the organization because it was such a company. As Hybritech grew, however, it had to begin imposing discipline on its labor force. It had to begin putting the interests and needs of the organization before the interests and needs of the scientists. When Tim Wollaeger joined Hybritech on April 1, 1983, to take over the post of chief financial officer, it became his duty to rein in the scientists when they began to lose track of budgetary constraints – partly because nobody else on the scene was willing to do it. Turning Hybritech into a place that would no longer be science-driven and scientist friendly, at least not all of the time, was a painful process. And it made some want to escape.

According to Wollaeger, the senior management at Hybritech had always been concerned with maintaining a supportive environment for the firm's R&D teams, perhaps to a fault: "Ted and David [Hale] may not agree with this, but I think they felt that they couldn't stomp on the scientists' creativity, so they never said no to them." Wollaeger tells of an episode involving David Hale and Joanne Martinis. Martinis wanted to expand the cell biology program. She requested funds to hire new people and build out new labs. Wollaeger reviewed the proposal, and discussed it with Hale. Together, they decided that new cells and antibodies were not priorities at that point in time, and that the request should be denied. Wollaeger describes what happened next: "I'm sitting in my office and Joanne comes out of David's office, and passes mine,

which is the next one, and she says, 'I got it.' And I said, 'Got what?' She said, 'David's going to let me enlarge my department.' I walked into David's office and I said, 'David!' And he said, 'Well, why don't you get together with her and talk about it.'" Because of the personalities and the routines that were established at Hybritech, the responsibility of enforcing added measures of fiscal discipline in Hybritech's approach to research and development fell into Wollaeger's lap when he joined. Wollaeger became what Hybritech needed, a chief skinflint who was willing to put a damper on the scientists' enthusiasm when he was approached for funds: "I'd always have to say, 'Well, we'd love to do it, but there's a budgetary constraint.' You know, 'That's a great idea that really big guys understand, but I'm just a bean counter. Sorry, I'm just going to have to tell you no.'"

By exercising his veto power, Wollaeger helped, indirectly, to catalyze the formation of Gen-Probe. In February 1983, Gary David, introduced a friend, David Kohne, to Tom Adams. Kohne was a biologist who had developed and patented a method for the in vitro detection of disease-causing microorganisms using DNA probes.[54] He was looking for help in raising money to commercialize his invention. Adams reviewed Kohne's work and was impressed. Along with Howard Birndorf, who was then acting as Hybritech's vice-president of business development (a job that included technology acquisitions), he approached Ted Greene with the idea of licensing and developing Kohne's technology. Birndorf recalls: "Tom took it to Ted, and then Ted went and talked to people. He came back and said, 'I don't think we

[54] David E. Kohne, "Method for Detection, Identification, and Quantitation of Non-Viral Organisms," U.S. Patent No. 4,156,729; issued January, 10 1983.

should do it. It's too defocusing. We're in antibodies and that's probes.'" One of the people that Greene had consulted was Tim Wollaeger. Wollaeger remembers the conversation: "I said, 'No way. We're going back to losing money if we do this. We can't go backwards. We promised all the analysts." Birndorf now concedes that this was a prudent decision: "It would probably have been too much for Hybritech to put under their belt." At the time though, he and Adams were convinced that the company was letting a prime opportunity slip away. "People were pissed," says Wollaeger. Adams and Birndorf asked the Hybritech board if they could make a private investment. The board approved their request, and in August of 1983, Adams and Birndorf formed Gen-Probe Partners. Each put in $50,000 to support Kohne's research for a year, and assigned technical milestones that they wanted Kohne to meet before proceeding further. Kohne achieved the goals. Says Adams: "Howard and I had a decision to make. We decided to leave and start Gen-Probe." Ted Greene had been afraid that this would happen. He remembers the day:

> Finally, Tom came to me and said, 'Well, I've got something I want to do.' And I said, 'Oh.' I remember I took him down, I had a boat down in Mission Bay, a trawler, and I took him down there with a six-pack of beer and just sat there and for hours and hours we talked about it, and there was no stopping him. So, I said, 'Alright, if I can't stop you from doing it, then I want to fund it.' And so, Hybritech put up the money to start Gen-Probe. We started out with a third of the company. Kleiner-Perkins came in, but we were really the lead investors.[55]

[55] Greene later explained to reporters why Hybritech had declined to take on DNA probes: "Monoclonal antibodies are to Hybritech what hamburgers were to McDonald's. Ray Kroc didn't move into chicken right away. He stayed with one major product until he was ready, and we'll stay with monoclonal antibodies for now." Dan Berger, "Hybritech Grows on Success of Its Diagnostic Work," San Diego Union, May 30, 1985; p. E-1.

There was little resistance to the idea at Hybritech. Adams explains: "David Hale was always interested in microbiology, because that's where he came from, BBL. He wanted to make an investment. So, it actually turned out that Howard and I left with two million bucks and a major shareholder in the form of Hybritech."[56] Kleiner Perkins put in $1.5 million. Gen-Probe was incorporated in June of 1984. The company went public two weeks before the stock market crash of October1987; its stock took a dive and never fully recovered, but technically, the company was a smashing success. Its diagnostics products have always done well in clinical testing markets. Chugai, a Japanese pharmaceutical house, purchased Gen-Probe in 1989 for $100 million. It remains one the largest employers in the San Diego biotechnology industry. Today, Tim Wollaeger claims to have played a part in starting the company "by not allowing it to be part of Hybritech." Hybritech had been obliged to recognize certain economic and organizational limits to its support of technological innovation, but Hybritech's entrepreneurs found a way.

Later, after Hybritech's sale to Eli Lilly, the new entrepreneurs who walked out of the company looking for things to do found themselves in a transformed environment, one in which both they and biotechnologies had been validated. In January 1986, on the impact of the merger on the biotech business, Edward T. Maggio, the CEO of Synbiotics, another early San Diego biotech firm, remarked: "The greatest vote of confidence we've seen was Lilly's takeover of Hybritech. That was

[56] In 1980-81, prior to moving to Hybritech, Hale was a vice-president and general manager at BBL Microbiology Systems, a division of Becton Dickinson & Co.

good for the whole industry."[57] A year later, Tim Wollaeger commented that the Hybritech deal, along with Bristol-Myers' acquisition of Genetic Systems, and reports from Genentech about progress in its laboratories and in the clinic, had put biotechnology "into the area of proven financial return for investors."[58] After Lilly came to town, Cole Owen left Hybritech to do start up a biomedical consulting business. He says that people had taken notice of Hybritech's gaudy price tag, and it helped him to attract business: "It was very fortunate for me, the success that Hybritech had enjoyed, and was still enjoying. I had a credible platform from which to talk to clients about what was moving, and what I was thinking was going to work and what didn't work in biotech."

Hybritech, and a few other successful biotech firms elsewhere, had remodeled the landscape of the pharmaceutical industry. In 1988, Brook Byers described the change that had taken place in San Diego: "There are venture capitalists crawling all over the place. I don't go down to San Diego without seeing someone at the airport visiting some company I never heard of. Ten years ago, I prided myself on knowing everything that was going on."[59] After Hybritech, there were a lot of things for entrepreneurs to do in San Diego. Previously, Ron Taylor explains, "All of the pharmaceutical companies had sort of always been big, I mean the Lillys, the Mercks, you know, the Schering-Ploughs – where were the start-ups? I mean, there weren't

---

[57] Michael Kinsman, "Leadership Scramble On: Biotech Companies Maturing," San Diego Tribune, January 27, 1986, p. P-29.

[58] Chris Kraul, "Venture Capital Focuses on Biotech," San Diego Union, Jamuary 26, 1987, p.45.

[59] Craig D. Rose, "Commuter Capital Goes For the Jackpot," San Diego Union, January 29, 1988; p. 2.

any." That was tough for those in the field who weren't suited to life in big corporations, and who had, for one reason or another, decided that they'd try to do it differently, if only they could:

> You know, we'd spent ten years or fifteen years working in the big companies, and they were, quite frankly, frustrating. But where did you go? You know, you didn't go out and buy McDonalds franchises, that was the only entrepreneurial thing that I can think of that there was in those days. We used to look, we used to read the Wall Street Journal all the time, and think of 'what could we do?' Well, in your field, you can't do much. And all of a sudden this biotech thing comes along.

And then there was Hybritech. And after Hybritech was gone, absorbed by Eli Lilly and Company, there were more entrepreneurs, people prepared by their experiences in science and industry to take advantage of new opportunities that were emerging in a new world. Ivor Royston had originally envisioned Hybritech as a place to work on a treatment for lymphoma. Following the acquisition by Lilly, it became apparent to him that the company would no longer be going in that direction, so he decided to start another one that would. "By 1986, I was convinced that lymphoma was an easier target [than other cancers that Hybritech was working on]. Lilly said no to lymphoma, so I started Idec Pharmaceuticals." Idec began with a technology licensed from Hybritech, a method for attaching radioisotopes to anti-idiotype antibodies. Birndorf (while still at Gen-Probe) and Robert Sobol, Royston's protégé at UCSD were also involved in putting Idec together, as was Kleiner-Perkins. Neither Royston nor Birndorf stayed directly involved with the company for very long. Kleiner-Perkins brought in Bill Rastetter from Genentech as CEO, and he built up the company in his own mold. In late 1997, Idec received clearance to start marketing the

first FDA-approved monoclonal cancer therapeutic, Rituxan, a treatment for lymphoma. Royston's dream had finally come true.[60]

Although he served on the boards of both Hybritech and Idec, Royston stayed on at his academic post at UCSD. He conducted cancer research at the VA Medical Center and the UCSD Cancer Center through 1990. By that time, though, he had become disenchanted himself with happenings at the Cancer Center and the School of Medicine. He felt that the university bureaucracy was moving too slowly in the development of the school's cancer research programs. He thought that he could do better. With the aid of friends in the local business community, he founded the not-for-profit San Diego Regional Cancer Center, which was renamed the Sidney Kimmel Cancer Center (SKCC) after a gift from the Kimmel family. Bob Sobol, his partner in cancer research at UCSD, and a co-founder of Idec, also left the university to become a principal investigator at the center. That same year that he organized the SKCC, Royston also decided to try his hand at venture capital. Forward Ventures began as a small firm with three partners, including Royston. It specialized in seeding biomedical start-ups. Royston's role was concentrated on technology assessments. The firm has raised five funds, each with better returns than the last, and can boast some major success stories. In 2000, Royston retired from science to enter the venture capital business on a full-time basis: "What I do now," he says, "is to use my experience from a quarter century of being involved with the biotech industry to help

[60] Rituxan was the second therapeutic product to emerge from San Diego's biotech industry. Agouron's protease inhibitor, approved in 1996, was the first.

other scientists develop their ideas and transfer technology out of institutes and universities into companies."[61]

Howard Birndorf left Gen-Probe in 1986 after a falling out with Tom Adams and David Kohne. He then signed on with a company called Progenx that had just been put together by Brook Byers, Richard Lerner, the president of the Scripps Research Institute, and Henry Niman, a Scripps scientist. When Birndorf arrived, Progenx had just gotten underway. Tina Nova was setting up a laboratory. After a few trips to Indianapolis, she had begun looking for a chance to get out Hybritech. It didn't take her long to find one. Brook Byers knew about her PSA work, and hired her to organize R&D at Progenx. An entire research group from Scripps was moved across the street to the General Atomics complex. After six months, however, it became clear that the technology (a technique for identifying oncogene protein products with monoclonal antibodies) simply wasn't working, and probably wouldn't make a viable product even if it could be fixed.[62]

---

[61] Ross DeVol, Perry Wong, Junghoon Ki, Armen Bedroussian, and Rob Koepp, America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions, Santa Monica, CA: Milken Institute, 2004, p. 24.

[62] Birndorf explains how the company came about: "Brook was cultivating Richard Lerner. Richard Lerner is the head of Scripps Research. Richard apparently came to him and said, 'I've got this hot technology, it's ready to be commercialized.' The real deal was, they just wanted to get this guy Henry Niman out. This guy was just a flake, it turns out. I didn't know that. So these guys negotiated this deal. They paid Scripps half a million dollars in cash with ongoing royalty obligations, and for that, they got these patent applications, Henry Niman, his group, and four hundred antibodies that had already been made came over to the company. So, Tina and I started at the same time, mid-January of '88, and we started, you know, hiring people, getting equipment, you know, there was some equipment there, and we were ordering equipment and hiring people and everything else, and we're going along and we're going along, and this guy, Henry Niman, he talked a language called Nimanese, we called it, because he talked and talked and talked, and you tried and thought you understood it, maybe, but then, when he was finished, you'd go back and say, 'What did he say?' We had to buy this big hundred thousand dollar camera, where, basically, he'd run these samples on gels, and he'd get a bunch of bands. And he thought you could get a pattern recognition of these bands and diagnose disease or, he even said he could tell the difference between male and female sex from pregnant women's urine, things like that. But it became very obvious very quickly, like after three to five months, I knew that

By chance, Birndorf then happened to meet Ron Evans, a scientist from the Salk, at a dinner party. Evans told him about his intracellular receptor technology. Birndorf thought it looked promising, took the idea to Byers and got Larry Respess, his patent attorney friend from Hybritech and Gen-Probe involved. They licensed Evans' work from the Salk, jettisoned the Scripps technology, and restarted under the name Ligand. Ligand was one of the first high-throughput drug screening firms to emerge in the late-80s. Industry people consider the patent protection that Respess erected around Evans' technology as a paradigmatic model for intellectual property strategy in biotechnology. Ligand has received FDA approval for mulitple therapeutic products. That qualifies the company for biotech celebrity. After seeing Ligand through its start-up phases as CEO, Birndorf left and began Nanogen, a company that is attempting to combine DNA probes and nanotechnology in 'lab-on-a-chip' diagnostic products. Birndorf had become a start-up artist, a serial entrepreneur. His expertise is in evaluating and acquiring technologies, setting up operations, and moving through successive rounds of funding toward a public offering. Birndorf has now been involved in seven start-ups. Brook Byers has invested in every one of them. Tina Nova followed Birndorf from Ligand to become COO. She then followed him to Nanogen, too, first as COO, and later as president. The company went public in 1997. Nova has since been involved with two new companies of her own.

---

this shit didn't work. I mean, he used to argue and say, 'See that band there?' And we'd all go, 'Where? There is no band there.' And he'd say, 'Yeah it is.' I mean, it was crazy. I kept thinking what the fuck, you know, what are we doing here? And even if it did work, how are you going to make it into a product? Is everybody going to have to buy this hundred thousand dollar camera? We couldn't standardize it, one gel to another. We tried putting markers in – Tina was doing a great job with this – but both of us came to the conclusion that this wasn't going to work. And I was trying to figure out what the hell to do."

When Ted Greene resigned his position as chairman and CEO of Hybritech in October 1986, he had already created a new job for himself. With the help of Henry Hillman, one of Hybritech's principal shareholders, he had put together a small venture fund, called Biovest Partners, that would specialize in funding early-stage biomedical start-ups. He brought in Tim Wollaeger, Hybritech's CFO, as a partner. In 1987 and 1988, Greene and Wollaeger seeded five new biomedical companies in San Diego – Amylin, Cytel, Vical, Pyxis, and Biosite Diagnostics. All were successful and eventually went public. By 1993, Biovest's initial $5 million fund had returned $130 million, and its companies had a combined market cap of over $2 billion. Biosite Diagnostics was founded by Kim Blickenstaff, Gunars Valkirs, Ken Buechler, Rick Anderson – the group that had become so disenchanted with Eli Lilly. Blickenstaff and Wollaeger had been friends for a long time. When Blickenstaff was presented with the idea of starting a new company by Valkirs, Buechler, and Anderson, his first stop for advice and assistance was Wollaeger. He asked if Biovest Partners would be interested in backing the venture. According to Blickenstaff, Wollaeger replied:

> 'I would. Let me check with Ted.' And he walked next door to Ted's office, because they were right next door, and he said, 'Ted, got a minute?' And he brought Ted in, and he said, "Ted, what would you think if Tim and Gunars got together and we funded them?' And Ted went, 'Great!' Ted was just, until you meet Ted, you don't understand it, but it was like, 'Absolutely. Not a problem.' And just like that we started talking about, OK, how much would it be?"

There was magic in the air again. Bill Crean notes that the new, post-Lilly, post-Hybritech environment came fully-loaded with social networks designed to facilitate the transfer of people, knowledge, and technologies:

> A lot of people got rich with the stock options when they turned to Lilly shares, and a lot of ex-Hybritech people started new companies, and the scientists said, 'Why not go to an Amylin, why not go to a Vical, why not go to a Gensia? If David Hale and Ted Greene did it once, I'll bet they can do it again,' and a lot of people bet on those personal relationships.

In the nearly twenty years since Lilly purchased Hybritech, the community built on such relationships has expanded, the networks have expanded, and the number of companies in the area has multiplied. David Kabakoff is now the CEO of a pharmaceutical company called Salmedix. To explain how his current company was staffed, he says:

> If you look at the employee base, I think pretty much every employee here has worked for at least one or more previous San Diego employers, with a few exceptions. We're located in town, so most of our employees have either worked at the university, or, even more of them, at other local companies.... As the community has grown up since the early 1980s, people who have been in one company have then moved to another company. I would say that within Salmedix, you have a fairly typical set of connections.[63]

AN ENTREPRENEURIAL CULTURE

Amidst the laboratories, ideas, technologies, capital, and companies around UCSD, the Salk Institute, the Scripps Research Institute, and San Diego's other scientific centers, there now exists a distinctive culture, an entrepreneurial culture characterized by its own practices, habits, beliefs, ideologies, values, and so on. In this culture, entrepreneurs don't quit. They don't cash out permanently. They keep going. Hybritech's group of scientific entrepreneurs did much to create the culture and they're still participating in it. They're still involved with founding new biotech

---

[63] Ross DeVol, Perry Wong, Junghoon Ki, Armen Bedroussian, and Rob Koepp, America's Biotech and Life Science Clusters: San Diego's Position and Economic Contributions, Santa Monica, CA: Milken Institute, 2004, p. 22.

companies in the area. Part of the motivation is money. When Hybritech was purchased and the vice-presidents deserted and began establishing their own firms, Royston remarked that it was to be expected – Lilly doesn't match startups, he said in providing "upside capital appreciation."[64] You can't get rich working for Eli Lilly and Company. Money is hugely important to San Diego biotechnologists. Professionally, they follow it everywhere. For most, making money is a personal objective, too. It has always been important to Howard Birndorf. He tells of flying on an airplane with Dennis Carlo, Hybritech's VP of in vivo R&D, shortly after Hybritech's IPO in 1981:

> We were flying back from the East Coast. We were on the plane, and all of a sudden, I got up in the middle of the plane and I started pacing back and forth up and down the aisle. And he said, 'What's going on? What are you doing?' And I said, 'I just realized I'm a millionaire. It was on paper, of course, but it was the fact that, all of a sudden, my stock was worth something. I don't know what it was, a million and a half dollars or something like that, and I was nuts. I mean, all of a sudden, it just hit me that my dream had come true. I was a millionaire before I was thirty years old, and it just blew my mind.

Birndorf claims to derive a good deal of personal satisfaction from his success: "Things really did change for me," he says. "I sold some stock and bought a house, and it was much more money and far bigger than I had ever intended. I bought a BMW, you know, I was becoming a consumer. And part of my motivation always was, really, to achieve some financial success." Once he had done that, he wanted more. He had experienced the capital and material gains that could be amassed by starting companies and getting founder's stock, and he wanted to keep going:

> That's one of the reasons I did Gen-Probe. Hybritech was public, I was not getting much more stock. At the time, they had this thing where you could do what they called a junior common stock, so we did this

[64] Craig D. Rose, "New President Charts Course for Hybritech: Indianapolis Commuter Says Lilly Merger Beneficial," San Diego Union, July 19, 1987, p. I-1.

> thing that was called series C common or something like that, and I got like fifteen thousand shares of this thing. It wasn't very much. I remember that there were x number of shares, and everybody got a little piece, and Ted got the huge piece, and I was pretty perturbed about that. It just didn't seem like I could any farther, really. I had what I had at Hybritech, and that was really all that I was ever going to get. I'd get little pieces, but I was making, not even a hundred thousand dollars a year then. My salary was low, so part of it was also money motivation, to make more money as salary, and I saw that at Hybritech, it wasn't just me, obviously, making that stock worth money, but the fact that I had started the company and received founder's shares.

Birndorf started keeping score with dollars, but eventually, he found that he simply enjoyed playing the game. He likes being an entrepreneur. So, he still chases dollars and never has enough of them:

> What's enough? I mean, I don't know. I'm still driven by that, by making money, I'm still driven by having toys and nice things. It's not as much anymore, though. It's different. How cars can you have? How many houses can you have? It's not the same anymore. I really do the things I do now because I really like them, and because it's still a real thrill to put something together and get it to work, and get the money, and the people, and the deals, and everything, and get public, and that really is personally what motivates me now. The money is nice, and it comes, but it's not the same as it was then.

Evidently, the rewards of entrepreneurship are hard fully to describe. When Ted Greene was asked why he had spent most of his career working so hard to get start-up companies off the ground, he replied:

> You might as well ask an Olympic athlete about what is fun about spending the kind of time and sweat they do to win a gold medal. You do it because you find something that is terribly exciting, and if you can make it work, it is something you can be extremely proud of – you're victorious.[65]

---

[65] Penni Crabtree, "A Magical Place: Hybritech Launched San Diego's Biotech Industry," San Diego Union-Tribune, September 14, 2003, p. H-1.

Greene explained his departure from Hybritech in October 1986 by saying, "I'm happiest working with a small group of people focused on a challenging technical and marketing opportunity. I'm not a big company man."[66] David Hale says essentially the same the thing: "Basically, I think what happened was that a lot of us had gotten used to being entrepreneurs and operating in a fast-paced environment. So, people were going. They decided that they wanted to go off and do this again." David Kabakoff says that, after being swallowed by Lilly, his recollections of Hybritech: "sort of left in me a desire to go back to that kind of environment, which I ultimately ended up doing, and others as well." Kim Blickenstaff likewise tries to convey that there is something special about working in a small start-up company. Of his time at Hybritech, he says:

> It was fun. It was exciting. I mean, I think it's those sorts of memories of how fun it was, how vibrant, that made people go off and do stuff like this again, because, you know, you want to recapture that sense of, oh, I don't know, boundless optimism, I guess, in the sense of, 'We can do it,' feeling the impact, knowing that you're making progress every day. I mean, it was a lot of fun. It really was. I mean, otherwise, I wouldn't be here. I'd go back to a big company if that was fun. It was a really neat atmosphere.

Tina Nova echoes these sentiments:

> The neat thing about Hybritech – you never know how great something is until after you leave, you don't know at the time – but the people there were phenomenal, and the amount of talent that was there, and the intelligence that was there, and the energy that was there. It was unbelievable. And we were all so young. We kind of forget about that. I mean, this was a really young group of people. And we were aggressive. We worked liked crazy. We loved what we did, and no one had to motivate us. It's just incredible that that culture existed.

---

[66] Chris Kraul, "He Wants to Duplicate Story of Hybritech," San Diego Union, October 23, 1986, p. C-1.

Some nostalgia may be coloring these reflections, but many people from Hybritech have founded new companies, and then, having set them on firm foundations, they've elected to move on to do it all over again. Like Howard Birndorf, they've become dedicated serial entrepreneurs. Jackie Johnson, Hybritech's chief molecular biologist, is one among them. In 1988, she joined Ted Greene at Amylin, and after building up that operation from just a few employees to a relatively large public company, she decided that she liked doing start-ups, and began looking for technologies and technologists, putting together business plans, and shopping them to venture capitalists. With Joy Koda and Caryn Peterson, two ex-Hybritech scientists who had followed her to Amylin, she founded Signal Pharmaceuticals, a signal transduction company, and DGT, a genomics company, with technologies transferred from the Salk and Scripps. In 1997, the three began FeRx with a magnetic drug delivery technology that originated in Russia. FeRx has a manufacturing facility in Colorado, near a base of relevant technical expertise at the Colorado School Mines. It is headquartered in San Diego, though, in order to remain in close proximity to capital and medical scientists in local institutions. The approach of the Johnson start-up and drug development team is to maintain new companies in more or less 'virtual' form – little more than a laboratory, a core group of researchers – until significant progress has been demonstrated in the clinic.[67] On why she does what she does, Johnson says:

[67] Investors, as well as entrepreneurs, have learned from experience in this culture. Johnson and other biotech executives say that, apart from periodic droughts and floods of risk capital, the funding environment for early stage firms has become more competitive. After some early giddiness in the market for biotech stocks, companies like Hybritech showed how difficult the process of drug development would be for small start-ups. Investors now generally want to see more evidence of scientific progress – clinical trial results – before putting in significant amounts of money into companies.

"I love it. Well, some days. We like drug development. It's fun, it's challenging, it's interesting, and possibly rewarding." What will she and her partners do if and when FeRx becomes successful? "We'll move on. The drug development team will move on."