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THE BILLION-DOLLAR MOLECULE

THE QUEST FOR THE PERFECT DRUG

BARRY WERTH

SIMON & SCHUSTER PAPERBACKS
1230 Avenue of the Americas
New York, New York 10020

This Simon & Schuster Paperbacks edition January 2014

Designed by Karolina Harris
Manufactured in the United States of America

20 19 18 17 16 15 14 13

The Library of Congress has cataloged the hardcover edition as follows:
Werth, Barry.
The billion-dollar molecule : one company's quest for the perfect drug / Barry Werth.
p. cm.
Includes bibliographical references and index.
1. Pharmaceutical biotechnology. 2. Vertex Pharmaceuticals Incorporated. 3. Pharmaceutical industry—United States. I. Title.
RS380.W47 1994
615'.19–dc20 93-32566

ISBN-13 978-0-671-72327-9
ISBN-13 978-0-671-51057-2 (pbk)
ISBN 978-1-4391-2681-3 (ebook)

FOR KATHY

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THE BILLION-DOLLAR MOLECULE

Courtesy of Vertex Pharmaceuticals

Joshua Boger

INTRODUCTION:
BEFORE THE BEGINNING

We live in an age of sequels. Many film lovers think the best sequel ever is *The Godfather: Part II,* and I support them. But the true impact of the second movie was to ensure from then on that no novelist, filmmaker, TV executive, documentarian, or record producer would ever again consider a major undertaking without weighing the opportunity to follow up, round out, and extend the original material into a multipart bonanza. But what of the original story, the creation, rooted in its time, foreshadowing—maybe—all that comes after it? Not just fun but instructive, a return to roots deepens our understanding, providing glimpses of the mature creature in embryo, so to speak.

In my latest book, *The Antidote,* I dramatize a twenty-year period, starting from when Vertex emerged as a promising but cash-starved start-up with distant ambitions to compete with the major pharmaceutical companies. The story climaxes with the company beating Big Pharma simultaneously in major disease areas, in a period of sweeping change throughout health care and society that even its far-seeing, charismatic founder Joshua Boger hadn't envisioned. How it survived that period (burning through nearly $4 billion) to mount a challenge to the old biomedical order just as that order was crumbling drives an account of ambition and hope,

hubris and Wall Street, ferocious competition and extraordinary collaboration, extreme highs and desperate lows.

What's amazing (to me at least) is how much of that story—its DNA, to use the obvious trope—is stuffed into this first book, coiled and ready to unfold. Here, for instance, is Boger, age thirty-nine, a year after defecting from Merck, commenting on his treatment by the world's biggest drug company, Glaxo, where executives listened to his proposal to collaborate on a program, heard his exorbitant demands, and promptly showed him the door: "Arrogance doesn't disturb or impress us. We understand arrogance." Or else here, in a meeting with Vertex's scientific advisors, an august group of a half dozen senior Harvard scientists, as he explained his plan to upend the drug industry by designing better drugs atom by atom. "What's to stop Glaxo from saying, 'Oh, oh, we see. Maybe we can do what you're telling us ourselves'?" someone asked.

"But they can't do it," Boger said.

"But Merck can."

"No, Merck can't either."

Boger's blunt assurance that he could do what Merck, the most admired corporation in America, could not, was creating on the fly a uniquely confident and ambitious research group. Throughout the time that I was there Vertex was more of a free-lance lab and privatized university-style consortium than a commercial drug business. Nearly everybody, including me, was younger than Boger, and it showed. The company was creating itself to conceive of and design and build small molecules better than the world's most skilled, profitable, and heavily endowed research organizations and what it took from the scientists was utter commitment, extreme passion, thrilling insight, and fearlessness. A volatile mix at any age, this is an especially strong brew for thirtysomethings, pent-up and wild to do the things that will distinguish them in life and launch their careers.

So remember the place was a research boutique, not a drug company. The differences are huge, as I immediately discovered when I realized in late 2010 that I wanted to go back inside. I approached Boger, and he discouraged me. Drug companies had become a favored target of federal prosecutors, and the companies were paying billions in penalties for defrauding government payers, bribing doctors and hospitals, marketing drugs for unapproved diseases, foisting antidepressants on nursing home patients, and otherwise trying to wring profits out of expiring product lines. Retired by then from Vertex, Boger told me he thought it would never let me back inside. It was Ken, his older brother and the company's general counsel, who convinced CEO Matt Emmens that it could manage the risk of having a reporter hanging around, and that I could be trusted.

I couldn't know in the fall of 1989 when I first wandered into Vertex's work in progress what I would see, much less that twenty-five years later I would return to publish a sequel. But I quickly found out that everyone there understood that it would take twenty-five years and possibly much longer to know whether they were really succeeding. Merck wasn't built in a day. The company became a research powerhouse in the forties and fifties, and only decades later became the paragon of the late twentieth century after its labs delivered a string of first in class and best in class pharmaceuticals. At its zenith, its stock spiked 500 percent in five years while it distributed free an unlimited supply of the drug Avermectin to cure African river blindness and began leading the way in developing treatments for AIDS. By that time, Merck was an organization, culture, and brand a half century in the making.

I've thought hard about how to situate this original story and its sequel among other well-known stories about American industrialists and the companies they built. Andrew Carnegie was thirty-five when he traveled to England in 1872, witnessed the Bessemer process for making steel, and "got the flash," as he liked to

say: came to understand that steel would replace iron for building railroads and bridges, which ignited him to "press inordinately" to build his own steel company from the ground up. Three years later he opened his first steel plant. In 1901, twenty-six years later, he sold Carnegie Steel to J.P. Morgan, allowing Morgan to create U.S. Steel and making Carnegie the world's richest man.

Thomas Edison moved to Menlo Park, New Jersey, in 1876, establishing his first full-scale industrial research laboratory, combining electrical and chemical labs with an experimental machine shop. He was twenty-nine. Three years later he invented the carbon-filament lamp, then three years after that opened new offices in lower Manhattan and started construction of the first permanent electrical power station. Throughout his forties, as he introduced the phonograph and a system for making and showing motion pictures, Edison labored to develop a method for processing low-grade iron for use by eastern smelters. The effort collapsed after the discovery of rich new mines in the Midwest. In 1901, twenty-five years after launching his Menlo Park "invention factory," its descendant General Electric organized the first modern R&D lab.

Nowadays the chief reference point for anyone charting the dramatic arc of an innovative company and its visionary founder is the triumphal three-act history—so established in the culture that it's become a meme—of Apple and Steve Jobs. Jobs was barely twenty-one in the spring of 1976 when he and Steve Wozniak started assembling Apple I computers in his family's garage. Nine years later, after introducing the Macintosh, he was stripped of control in a palace coup, then returned to Apple more than a decade after that, when he was forty-two, to rebuild the company. In 2007, in his most memorable keynote presentation ever, Jobs unveiled the iPhone with its life-altering touch-screen interface: the Emancipation Proclamation of the mobile revolution.

In the time of Siri, we forget how different life was before Jobs

and others transformed modern communications. I remember my delight, before the emergence of the Internet, when I realized in 1990 that Vertex's negotiations by fax with a Japanese partner were proceeding twice as fast as if the other company was located across the street in Cambridge. It worked like this: chief business officer Rich Aldrich would feed a document into the machine as he was leaving work; his Japanese counterparts would receive it just as they were arriving for the day, then revise it until they left that night. And so on. In other words, while Aldrich and America slept, the spinning earth accelerated discussions that in the same time zone would have to wait till tomorrow.

Then there's this gem, from when I mention on page 158 of this book that instead of sending around paper memos, Boger had begun notifying the scientists "via electronic mail (email)." Vertex is older than e-commerce, the human genome, and the mobile age. Boger is sixty-one. Neither he nor the company has gotten anywhere near as rich, famous or influential as history's great business titans and their industry-shaping corporations. I'm not necessarily putting Boger in the same category as Carnegie, Edison, and Jobs, nor am I putting Vertex on a plane with U.S. Steel, General Electric, and Apple.

But I'm not counting them out either. (Perhaps my third book about Vertex, reported on eighty-five-year-old legs, beamed directly from my brain into God knows what kind of personal device, published globally in 2039, will have something to add here.) As protagonists in an evolving story, Boger and Vertex in volumes one and two have cleared a key threshold. The company is now solidly a drug company, with two major, pathbreaking successes to its credit and a multibillion dollar franchise with a long, prosperous business cycle ahead of it. Just as in *The Godfather* Vito Corleone builds the family business in the first picture so that his son Michael can leverage it in the second, Boger has handed Vertex to others to drive ahead.

While I was researching *The Antidote,* I tried to describe what I was doing and feeling. I told people: "It's like I was in the garage with Jobs and Steve Wozniak, and now I'm watching from backstage as Jobs introduces the iPhone." Will Vertex go on to become the world's most valuable company, as Apple has done since then and after Jobs left the scene? Most likely not, though it's surely possible, and as Boger likes to say; "Until something is not a possibility, it's a possibility." Frankly I don't think that matters now, at least for reading purposes. I think it's fair to summarize at this point that Boger's quest from the minute when he sat at his whiteboard at home in New Jersey and summed up his goals (*Make better drugs faster: Become Merck, but better; Build the 21st century pharmaceutical company*) until the approval of Vertex's breakthrough cystic fibrosis drug, Kalydeco, ranks with those of other heroes of American business. So far.

If Boger and Vertex warrant specific comparison it would have to be with George Merck and the family-owned fine chemical company that he turned from a vitamin business into what *BusinessWeek*, around the time this book was first published, crowned on its cover "The Miracle Company." Unlike Boger, Merck wasn't a scientist, but he saw that patient-focused R&D was the future. Like Boger, he surrounded himself with people who could make the future happen. In August 1952, he appeared on the cover of *Time* magazine over the heading, "Medicine is for people, not for profits." He was lauded for his altruism, but George Merck was also canny, adding: "If we remember this, the profits will follow."

Vertex arose directly out of this lost two-part wisdom. It has been Boger's point precisely from the day he left Merck and started on the long road to building a drug company. I went back inside Vertex in 2011 because I wanted to see what Boger's vision had produced. I'd been fascinated once by the sheer audacity of it, and what I saw when I returned resembled—to a remarkable degree—the picture he had first painted for me, back before the

Gulf War and the dot.com revolution and the rise of blockbuster biologics and the cost crisis in health care and the yawning self-doubt that seems more and more to grip the national psyche.

The Billion-Dollar Molecule records Vertex's daring beginnings up against crushing odds. *The Antidote* tells the story of how it emerged to become a touchstone of American innovation. Where the company goes from here we don't know, but what sort of force it will be in the industry and the world will depend primarily on what happens in the labs—whether the original company spirit, forged in its early days, survives.

Stay tuned.

Barry Werth
Northampton, Massachusetts
September 5, 2013

PART ONE
THE STORY

CHAPTER ONE

Squatting between the twin towers of the World Trade Center in New York City, the Vista International Hotel is a minor cultural monument of the 1980s. Elsewhere it would seem a standard modern luxury hotel—contrived public spaces (schooners in the Tall Ships Bar, sail sculptures on the mezzanine), penthouse pool, chrome chandeliers—but here, dwarfed by shimmering behemoths at the foot of Manhattan, it looks like a chunk of brushed aluminum wedged between the prongs of the world's biggest tuning fork. Few of the hotel's guests seem to notice. Overnight visitors to the Vista come to New York not for the city's cultural and aesthetic smorgasbord, three miles uptown, but because, when it opened in 1982, the Vista was the first hotel in 155 years to be built near Wall Street. Less gaudy than the Taj Mahal in Atlantic City or Circus-Circus in Las Vegas, but equal to them in purpose, the Vista was constructed expressly so that guests can roll out of bed and be where the money is.

In the fall of 1989, the money on Wall Street was famously skittish, and first-time pilgrims to New York's financial markets most often came away disappointed, making the Vista a kind of Heartbreak Hotel for entrepreneurs. The stock market, despite record highs, was still shaken and defensive two years after the crash of 1987. With a recession looming, investors had withdrawn to the safety of big companies with solid earnings. Worried about liquid-

ity, they "lightened up," especially on new companies. Such companies were too risky, it was said. They burned money. It could be years—decades—before they paid out, which by Wall Street's myopic perspective was past the vanishing point. As with many collective judgments, Wall Street's gloom was rapidly self-fulfilling. As investors retreated, stock prices sank, weakening the new companies and making their need for money all the more dire. The situation was widely considered a national tragedy by those who thought America's future competitiveness was being squandered in Wall Street's unwillingness to invest in emerging technologies. Of course, the same was said by the architects of the new companies themselves.

Yet still they came. On a warm morning in mid-October, the chief executive officers (CEOs) of more than forty new biomedical companies took their places behind several rows of long cloth-covered tables in the Vista's ballroom, unhopefully partitioned for the event. Of all the emerging fields Wall Street was cool about, biomedicine was by far the most worrisome. It spent the most money, took the longest time to pay out, and even its successes like Genentech, whose hysterical debut on Wall Street nine years earlier had driven the company's stock price from $35 to $86 in the first hour of trading, were wanting. The conference itself was an attempt to revive interest in the field. Throughout the morning, the CEOs each would have five minutes to introduce their businesses to an audience of about 150 presumed investors, although, as many of them already had discovered unhappily from perusing nametags around the coffee urn, there were few real investors present. Sellers outnumbered buyers at about the same rate, and with the same dissonant hopes, as girls do boys at an afterschool class in social dancing.

In such a market and with so little time at the podium, most of the speakers shed all pretense; it was impossible to be too bald here. Many had already filled out forms detailing their company's most intimate financial needs that owed more to newspaper personal ads than *Barron's*. "MARKET OPPORTUNITY:" flashed a California man's slide, "Thrombosis—Leading Cause of Death in the Western World."

Joshua Boger sat impassively through the morning session,

silently rehearsing his speech. As founder, president, and chief scientific officer of Vertex Pharmaceuticals Incorporated of Cambridge, Massachusetts, Boger's titular weight exceeded most of the others' on the program. But his plight was identical. Ten months earlier, he and a partner had launched Vertex with a coast-to-coast tour of venture capital companies, racking up 100,000 frequent flier miles in three months and raising just under $10 million. Vertex had no products, no revenues; it would be years, if ever, before the company would know if it even had something to sell. Yet it already was spending $75,000 a week even though its unfinished labs were crammed to the ceiling with unopened crates; even though, as the history of such companies showed, it would take up to a dozen years and more than $250 million to develop its first drug. None of this had discouraged Boger, who was thirty-eight, from coming to New York at a time when hundreds of decisions clamored for his attention back home. On the contrary, Vertex's harrowing financial need was the sole reason for his making the trip.

Six feet five inches tall, Boger (pronounced with a hard *g*) was dressed in the uniform of the day—dark pinstriped suit, jacket buttoned below the sternum—though he appeared just rumpled enough to suggest that such clothing was neither his preference nor his habit. He was long boned though not ungraceful, sitting with his legs characteristically intertwined and his torso bent forward from the waist, like a dancer's. Only his hands, which were large and torn at the cuticles, moved, thrumming a clean white pad on the table in front of him or twisting a ball-tipped marker. His face was a mask of serenity, a broad oval rising to a wide glimmering forehead and capped by thinning stick-straight brown hair that Boger parted anomalously on the right. Though he wore thick, rimless glasses and a beard that was not trim, it was not hard to imagine him as a ten-year-old—a caricature of a young scientist—grin, bones, and cowlick all askew.

Speaking just ahead of Boger was an irrepressible woman in her thirties who four years earlier had started a home delivery service for prescription drugs and whose candy-apple lipstick offset a cumulus of frosted hair. Her company, American Prescription, Inc., had grossed $185,000 in its first year, $900,000 in its second, and was now projecting sales of $70 million by 1993. "It's been an ab-

solutely incredible history as the company continues to ramp," she gushed.

Boger, mindful of Vertex's situation, ringingly agreed. "I hate," he said, taking the podium, "to follow someone with sales."

A chemist by training, Boger had come to selling solely as a requirement for doing science. But there was no mistaking, as he began to speak, that he seemed born equally to both tasks. He had grown up in a thriving, prosperous household in Concord, North Carolina, twenty miles northeast of Charlotte, a scion of the German and Scotch-Irish pioneers who had dominated the area since before the Revolutionary War and are known to be self-reliant, industrious, unemotional, opinionated, and cold, although, as North Carolina historian William Powell points out, loyal to family and friends. His English ancestors on his mother's side, the Sneads, who descended the Piedmont by way of aristocratic Virginia, go back to the Domesday Book.

Correctly Southern, both the Bogers and Sneads have a history of carefully cultured, small-town respectability; both have long been prominent in their communities. Boger's paternal great-grandfather, a farmer in Concord, was wounded four times in the Civil War, including once at Gettysburg; his grandmother was active in the Daughters of the Confederacy until her death in 1960. His father's father, after serving as superintendent of the segregated Cabarrus County school system, took over the primitive Stonewall Jackson Manual Training and Industrial School in Concord and made it into a model reformatory, largely by preaching a stern progressivism and persuading mill owners from around the state to donate heavily for new buildings.

Boger's father, Charlie, a tank commander in World War II, was self-employed as a yarn broker. Inheriting from his own father a genuine interest in people and a practiced Rotarian appreciation for knowing what others want and how to give it to them, Charlie Boger was an exceptional salesman. With the textile mills of the Piedmont expanding headlong in the years after World War II and the explosion of new synthetic fibers and dyes, mill operators were drawn into the briskest competition they had ever known. Boger, who had a degree in chemistry, often went to sleep at night studying chemistry texts, so that when he drove to the mills in Char-

lotte, Kannapolis, and Winston-Salem, occasionally with one of his four sons on the front seat next to him, he could explain exactly what chemical steps would be necessary to capture the fashion industry's latest colors on any type of thread. Buyers were impressed, and Boger was popular, especially with the product men, who valued his expertise and the considerable work he saved them.

But Charlie Boger sold better than he managed. Thirty years later, Joshua would remember making customer calls with him during the summer and being shocked to find that he had signed flat-rate annual contracts. The busier his father was, Boger realized, the higher the percentage of his labor that went to others. Petulantly, Joshua grew disdainful of people who allowed themselves to be exploited this way. Though the family lived comfortably, Mary Snead Boger, Joshua's mother, never ceased to worry about money—a permanent cloud on an otherwise untroubled and equable horizon. "Charlie could sell you anything," she would recall years after her husband's death, "but he didn't know bat brains about business."

Shortly after Joshua was born, the family, riding the fullness and confidence of the postwar boom and the promising start of Charlie's new business, moved from a duplex in the center of town to a large, custom-built Georgian Colonial on a newly subdivided dead-end street on the outskirts of Concord. With two-story wooden columns grafted onto a brick facade, the house, eventually stuffed with a hefty flotilla of solid English reproduction furniture and 10,000 books, sat on a small rise, like a prow, facing a country club to which the Bogers belonged. It was nestled by a broad lawn dotted with magnolias and encircled by fields and pine woods with a stream that the boys could fish in—the complete New South idyll.

Boger grew up in the house in a whirl of boyish overachievement. He and his three brothers each excelled in school and in sports. Each was tall, thin, and high-spirited and had voluminous interests, making the household a kind of boisterous, high-expectation boarding school with Boger's mother, an outspoken and dramatic woman, as headmistress. With her liberal encouragement—later to become an award-winning theatrical director, she once marshaled other women to block the razing of Concord's antebellum courthouse by standing in front of a bulldozer—the boys relentlessly prodded

themselves and each other. Together they became famous in town, the "Boger boys" being Concord's answer to the precocious "whiz kids" of the 1950s and 1960s. When Joshua was ten, he had progressed so far in a year of piano lessons that his teacher pronounced him a prodigy and contacted the local newspaper. In an article picked up by the Associated Press, Boger explained that he practiced every morning at 6:30, before school, and had begun charging forty cents a week to teach his brother Ken, who was five years older. "I keep him behind me," he said, "so I can keep up the lessons."

Diligent at everything he tried—he handed in a 400-page paper on Africa in the fourth grade—Boger gravitated early to science. By age seven, he was spending hours, and sometimes days, in a laboratory that his father helped him build above the garage. It was a low-ceilinged barnlike space with unpainted rafters and plank floors—"more space per scientist than we have at Vertex," he would joke—and it reflected the eclecticism of his world, a world that young Boger self-assuredly considered *the world* and thus strictly within his power to control. In one corner there would be a potassium permanganate crystal the size of a dinner plate suspended on a thread over a vat; elsewhere, a stack of microbiology plates, the result of a recent experiment in which he had swabbed the throats of the other kids in the neighborhood in order to compare the germ-killing potency of mouthwashes. There would be plants growing, animals in cages, rocks that Boger had chipped out and mounted on boards, chemistry experiments from a Time-Life project series that his father had ordered through the mail, a microscope with a fly impaled under its lens. Whatever order there was reflected the materials on hand and what Boger called his "dumbcat curiosity." Other than the rows of shelves groaning with the family's extra books, the space was his alone. His father might donate reagents—he once came home with twenty-five pounds of mercury, handing it over without a word—but neither of his parents ever visited.

As a young experimenter, Boger simply went his own way. Once, when he was eight, he spent a long Saturday shuttling between his lab and an open red-clay field next to the golf course. Knowing that water, Drano, and the tinfoil from a milk bottle produced hydrogen, he filled several balloons with the volatile gas. Heedless of

the fate of the Hindenberg, he then ran a mouse through a maze he'd constructed, built a gondola to take the hapless animal aloft, and sent it soaring. When the mouse came down, Boger again subjected it to the maze to measure its disorientation. Being eight, he spent the next day playing baseball.

To Boger, science was the most natural way of apprehending a world that could otherwise be maddeningly obscure; he was enthralled with its precision and power. It was also fun, just as lying under twelve feet of water in the diving pool at the country club was fun. But science had its imperatives. In a school essay that he wrote at age thirteen in which he traced his academic career from kindergarten, which he recalled enjoying "except for rest time," up to the eighth grade, he concluded purposefully, "Recently my interest in chemistry has turned me towards the field of medical research. My goal in life is . . . to help rid man of the burden of disease and hunger, and to help man get along with man."

It was this trajectory, launched in puberty and accelerating more or less along the most favored path ever since, that brought Boger now to the speaker's platform at the Vista. Valedictorian in high school, he went on to Wesleyan University in Connecticut, where he trained under the legendary Max Tishler, one of the most important and prolific figures in the history of drug research, and where he again finished first in his class. One of only eight students nationally to receive a full four-year National Science Foundation fellowship for graduate school, he then went to Harvard, which then as now had the best organic chemistry department in the world, where he got his Ph.D. He ultimately went to work for Merck and Company, the world's premier drug firm. By his mid-thirties, an age when most chemists are still making compounds at the bench, he had become Merck's senior director of basic chemistry. He held seventeen patents, although none for an approved drug, and was considered among those who knew the company best as a favorite eventually to head Merck's vaunted $1 billion annual research effort—perhaps among the most powerful biomedical posts in the world. They were stunned—some furious, others relieved, even overjoyed—when Boger abruptly left the company in early 1989 to found Vertex.

Boger was never breathless as a public speaker, but he had trained

himself, when talking to businesspeople, to be low-key and earnest. His years in the Northeast had purged all but the last traces of southernness from his voice, which remained sonorous and steady. Yet what set him apart now, as he described his company, was the strength of his pedigree. Everything in his past had led to his being a prince of the industry he now hoped to revolutionize, and it gave him a powerful mien. It was the aspect of the favored son, the smartest kid in the class, in the school, maybe in the school's history. Even at the Vista, Joshua Boger had valedictorian written all over him.

Vertex, Boger said, was not only about to create powerful new drugs, but also to change the way all drugs would soon be created. With only five minutes to speak, he could hardly explain the scientific rationale for such a statement. He referred fleetingly to Vertex's "unequaled scientific staff" and the "most impressive set of . . . technologies in the world." Beyond that, he quickly summarized the company's first project. It was an attempt to improve upon an experimental drug called FK-506 that suppressed the immune system. The drug had been shown to be highly toxic in some test animals, but it was still thought to have extraordinary potential in humans in facilitating organ transplants and curing autoimmune diseases.

"We will redesign the molecule," Boger concluded matter-of-factly, "and eliminate its undesired properties."

Afterward, Boger left the ballroom as soon as he could politely pull himself away. He had never expected much from this forum; Wall Street's "promiscuous imagination," as biotechnology writer Robert Teitleman called it, had long since grown impatient with stories like his, and the shortage of real investors at the Vista had proven that. But Boger knew something else. Vertex was in a historic position. The company was attempting something so bold that most people in the drug industry questioned whether it could be done at all. It would design drugs—not merely appropriate them from nature and tinker with them, as was the rule, but design them, atom by atom, as one designed a skyscraper or a computer.

As even Wall Street might have recognized, if Boger was right, the most consistently profitable legal industry in America during the past forty years (besides, perhaps, cigarettes) was on the verge

of an upheaval in the way it went about discovering new products, an upheaval that would vastly increase the utility and variety of those products and the oceans of money that flowed from them. Over the next thirty years, Boger believed, drug research would become vastly more refined, more rational. Those who led the way would be heroes. Vertex, he knew, or some company like it, could well become the new Merck, which besides being a paragon of medical science had recently become, as measured by virtually every magazine executive poll, the most admired corporation in America. It was a prize of rare stature and importance.

And for that, Boger had decided, no task was too onerous, even putting himself out for as unpromising and unseemly a cavalcade as the one at the Vista.

"A meat market," he described it later. "We're talking fishnet stockings. I mean it just doesn't get any lower than this."

CHAPTER TWO

Ever since Harvard survived its first headmaster, Nathaniel Eaton, who beat students with a walnut cudgel "big enough to kill a horse," and became what historian Richard Norton Smith calls the "epicenter of American education," Cambridge, Massachusetts, has been a place where a disproportionate number of the world's smartest people come to prove how smart they are. Against this elite testing ground chafes another Cambridge, a minor, graying northern city in which generations of immigrants and African-Americans have lived crammed in underheated triple deckers and toiled in scores of shoe and candy factories, foundries, and machine shops. Until World War II, the city was roughly split: Harvard and MIT on the east and west and along much of the Charles River, working-class Cambridge in between and in the industrial flats across from Boston and Charlestown. Then history lurched, and Cambridge tilted. The universities, supported by the federal government's ambitious research programs, began pushing relentlessly outward. Manufacturing died or moved away, along with those it employed. Most critical, knowledge became a big business like any other. As Harvard's Sumner Slichter has observed, "The discovery that an enormous amount of research can be carried on for profit is surely one of the most revolutionary economic discoveries of the last century." It was during this period that the people arriving in Cambridge to prove themselves, partic-

ularly in the sciences, added to their prerogatives the takeover of the city's industrial real estate.

Along lower Sidney Street, an area of low-slung factories and warehouses abutting a necrotic rail yard, the overlay of the new Cambridge and the old is striking. On one short block, across from each other, are the Boston Pipe and Fittings Company and American Foundry, Inc.; within one hundred yards, in similarly drab two- and three-story brick buildings, such futuristically named companies as ImmunoGen, Bioprocess Technologies, and Holometrix. The barrackslike former St. Johnsbury Trucking Company depot, until the early 1980s a hub of grinding gears and hissing airbrakes, now produces X-ray telescopes in sleekly refurbished anonymity. Despite its new association with Harvard and the Massachusetts Institute of Technology (MIT), the presence of so many exceptional scientists, the restless incubation of so much profit motive, and the influx of so many Saabs and Acuras, the area remains dolefully nondescript, a temporary address for the new companies and a final one for the old.

Vertex started leasing 10,000 square feet in a former construction company warehouse at the corner of Sidney and Allston streets in April 1989, six months before Boger's outing at the Vista. In keeping with his ambitions, he began to look at once for more space. The building is brick, one story, nearly square, and the occasional target of graffiti. When it was built in the 1920s, it had mullioned shop windows and ersatz Corinthian columns. Sixty years later, the columns were stuccoed over and the windows replaced with thermopanes, giving the building an air of cheap recycling, like a motor vehicle bureau that once was an armory. In fact, the windows are as superfluous as the columns. Because anything of use to a legitimate drugmaker is of substantially higher value to an illegitimate one, the company prefers not to advertise the contents of its labs. Its blinds are all but permanently drawn.

Boger was still living in New Jersey, near Merck's giant central research campus in Rahway, when he decided to locate his then-unnamed company in Cambridge. He intended Vertex to be highly visible from the start—to the international elites of business and science, if not to pedestrians—and for that, he thought, Cambridge offered a powerful showcase.

Businesswise, it was a singularly unpromising time. During the previous decade, nearly 200 biotech businesses had sprung up, yet only one, Genentech, earned a regular profit, and even that was disappointingly small. Most of the companies had simply gone on hemorrhaging money, blindly, with no end in sight. Dozens were now failing or scrounging for buyers.

Add to that a billowing national recession and a comatose New England economy, and Boger's decision to leave Merck and set up in borrowed offices in Cambridge in the dead of a lightless New England winter seemed fateful. Boger was anything but. The previous fall, he'd been recruited by an irresistible California venture capitalist named Kevin Kinsella, an embodiment of that flamboyant breed and originator of Vertex's concept, and together—Kinsella on the West Coast, Boger on the East—they'd plunged ahead. Working from a ninety-page business plan that Boger had composed in less than four weeks, they knocked on doors relentlessly, talking with investors, scientists, vendors, developers, lawyers, contractors, regulators, and potential partners, leveraging commitments pyramidally. "Don't you think this is five years too early?" Boger was often asked, to which he answered, brimming with impatience, "Yes. But five years from now it'll be five years too late." It was a determinedly Cambridge answer, smug, marbled with arrogance and risk. But by then, they'd enlisted perhaps the one academic collaborator who could match Boger's pedigree, ambition, intellectual firepower, and cachet, Harvard wunderkind Stuart Schreiber. How, Boger and Kinsella wondered, could they lose?

This was Boger's other reason for choosing to be in Cambridge. Every young biomedical company needs in the absence of its own science the association of big-name researchers—a scientific advisory board (SAB). Most SABs are ballast for the letterhead. Boger professed to want an SAB that was more than that. Having identified as his optimal SAB five senior faculty members at Harvard and having gotten them all, most notably Schreiber, he intended to use them. Being in Cambridge meant having them within courier distance.

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On the Saturday morning before Boger went to New York, Vertex's SAB and its staff scientists huddled for the first time in the company's makeshift lunchroom. Billed as an all-day strategy session, the meeting was also a critical first test of Boger's determination to use the SAB. As with the start-up of many high-minded adventures, there was the usual air of self-selection reinforced by deprivation—a mercenary, albeit ragtag, flavor. It was the first time some of them met.

In aggregate, they were the kind of people Boger felt most comfortable with—young, male, irreverent—people like himself. Of the twenty researchers on hand, just two were women; only five were over forty. Yet despite their relative inexperience, each had sacrificed something to be here, as the setting reminded them. For weeks, jackhammers had rocked the building, leaving a pall of cement dust on books, boxes, clothes. Overhead, ceiling panels had been left out by workers, and skeins of unattached pipes stood exposed. The screen on which Boger presented a fuller version of the slide show he would take to New York was gray, steel, battered, and part of a short-term leasing agreement, as was the furniture in his office, which opened onto the lunchroom and had mounds of books and catalogs splayed chaotically along every wall. Many of the scientists were accustomed to being pampered at such meetings: Merck, where some of them had previously been associated, picked up visiting researchers by limousine and toured them around by helicopter. Lunch today at Vertex would be pizza and Greek salad served on paper plates.

In fact, the close involvement of the SAB was an unpopular idea of Boger's that would require considerable selling within the company. Scientists in industry and scientists in academia tend to be brutally dismissive of each other. Academic researchers thrive on publication, attention and credit being oxygen to their careers. Yet to industrial scientists, whose own success most often depends on keeping their best work secret and who are less well known, most academics are recklessly, inexcusably self-serving—loose cannons. Boger had brought to this room some of the best industrial and academic researchers in their fields. Getting them to talk openly would be another matter.

The problem had first surfaced a week earlier, pungently, ominously, not a surprise, but sooner than most expected. Schreiber, a slender, enthusiastic thirty-three-year-old chemistry professor, had mildly proposed at a smaller meeting that everyone discuss what experiments they were planning.

Coming from Schreiber the suggestion was hardly as innocuous as it seemed. He, more than anyone else at Vertex, was Boger's equal, his other: a fast-rising star who, with the backing, position, and control he had long conceived of and only just won, was beginning to make his mark on a world stage. There were other similarities. Like Boger, Schreiber is a chemist and an avenger for the Harvard legacy, long in disfavor, of exalting chemistry above all other life sciences. He is a quick, copious thinker who can see past his own field and direct a swarming, multifrontal research effort. Schreiber worked seven days a week, had a big group of the world's most ambitious graduate students and postdoctoral fellows, published furiously, and could smell a hot idea. "Stuart is fearless," Boger once said admiringly. "He has a killer instinct for doing the right experiment."

He could also be disarming. Like Boger, Schreiber exudes an easy border-state affability: He grew up at the high end of a semirural gun-and-dirtbike culture in east-central Virginia, a few hundred miles from Concord, and partied his way through high school before discovering chemistry in college. He wears imported loose-fitting tweeds and soft loafers and commutes to Cambridge from his five-story townhouse in the Back Bay in a gunmetal gray Porsche 911 with a car phone. With a smooth and eager face, respectful manner, and large swimming eyes magnified aquatically by round wire-rimmed glasses, he looks more like a successful young art dealer than one of the two or three most promising organic chemists in the world. "Eddie Haskel," one Vertex scientist calls him.

Like Vertex, Schreiber's group at Harvard was studying drugs that suppress the immune system, a field that was rapidly heating up in large part because of Schreiber's own work. Angling sharply for what academic researchers want most in such new areas—priority, acknowledged leadership in the field—he was concerned about being slowed down by overlapping effort.

"I think it's best that we consider what we'd like to do immediately and what Vertex would like to do," Schreiber said.

There was a palsied silence, the Vertex scientists all looking tentatively at one another or at their shoes. Finally, Boger brushed aside the question by saying how many people he planned to hire and in what disciplines—a coded message that indicated the general direction of Vertex's research but no specifics. Though Schreiber was being paid $25,000 a year to attend perhaps a dozen such meetings, owned 150,000 shares of Vertex stock, and had been recruited largely for the benefit of sharing information and materials with his lab, it was clear he was not going to be fully trusted as a collaborator, not even by Boger. Sensing he would get no further, Schreiber said, "OK then, on the table, anybody who gets to an experiment first should do it." With everyone agreeing, the conversation moved uncomfortably on.

With the labs still unopened, it was too early for the threat of such competition to arise among Vertex's own scientists, but here, too, were tremors. Boger had recruited an exceptional group of researchers; of the company's ten most senior people, all but one had worked at Merck, Harvard, MIT, or Yale. Moreover, Vertex planned to integrate the most advanced disciplines of molecular biology, which deals with function, and of chemistry, which addresses structure and mechanics—whose practitioners, like behaviorists and Freudians, have little good to say about each other. Already the company had more submicroscopic disciplines—medicinal chemistry, X-ray crystallography, nuclear magnetic resonance spectroscopy, molecular modeling, computational chemistry, protein engineering, protein chemistry, enzymology—than a small university, and competition over hiring and lab space had grown fierce. As in war, victory in science is measured in bodies, territory, and materiel, and Vertex, it seemed, would be no different. Coupled with the personal ambitions of those who saw Vertex as a major drug company in the making and themselves growing in power and influence along with it, a secondary ambience of intramural squabbling had already begun to poke through the initial looseness and camaraderie.

Now, in the lunchroom, Boger moved to unite all sides. Far from being disturbed by the general testiness, he considered it affirma-

tion that his ideas about corporate culture—a culture of enlightened self-interest—were taking root. Boger wanted people who were unbowed by competition; people who, like himself, insisted upon being best. He wanted an orgy of bristling, militantly selfish creativity of the kind he grew up with. "Arrogance doesn't disturb or impress us," he once said in another context. "We understand arrogance." As with much of what Boger said during this period, the remark seemed at least partly calculated, like a short man's swagger, to compensate for certain disadvantages: Vertex, despite its talent, would be competing against labs that were vastly richer and more experienced; outsized, even outrageous, boasts were good for morale.

And yet Boger also believed, or seemed to believe, every word he said. Devoutly irreligious in his personal life, he had a faith in himself and in science that was Himalayan, towering over most other people's. Boger's convictions were huge, and he expressed them with such confidence that it was hard not to agree with him.

Boger chose not to make the case for cooperation himself. Instead, he turned the meeting over to Rich Aldrich, Vertex's vice president for business development. Aldrich, a tall, curly-haired thirty-five-year-old with an M.B.A. from Dartmouth, was the group's sole layman. His ancestors arrived in Plymouth in 1630, ten years after the *Mayflower*, and have been ensconced in the state, in law and banking, ever since. Within those staid Yankee confines, Aldrich's decision to put his career in risky biomedical start-ups marked him as something of a family rebel. But that didn't grant him instant acceptance among the scientists in the room. On the contrary, many of them, even if they didn't know his background, viewed him as a political and cultural nemesis, a "suit." Aldrich, who was dressed today in khakis and a blue oxford shirt, enjoyed turning the disparity between business and science back on them directly. "Design any drugs lately?" he'd ask.

Despite their differences, everyone at Vertex had one thing in common. Under the terms that enable impoverished, unknown companies to recruit top scientists and expect them to work Saturdays, they'd all begun to amass large amounts of stock—from 10,000 shares for a junior scientist to, in Boger's case, 780,000 shares. These holdings were at present worthless but would likely

make them all rich if and when the company went public, and extravagantly rich if Boger was right and Vertex became a major drug company. In Boger's view, this shared fortune was so obviously compelling that no one need be reminded of it; it should automatically restrain even the most rapacious ego. And indeed, as Aldrich now began to discuss the company's plans for raising the tens of millions of dollars it would need over the next couple of years, the scientists' collective attention focused as sharply as a team of accountants'.

Aldrich told them that Vertex was considering a range of options, but the most promising were its discussions with other drug companies. Vertex had approached eight other companies about the possibility of their underwriting part of its research in return for certain "downstream" development rights. In other words, he and Boger were aggressively talking with potential competitors about the company's science even before it had unpacked its first test tubes. Standard practice, the discussions nevertheless startled some of the group's academicians.

"Isn't one in danger," drolly interrupted Jeremy Knowles, a brilliant and much admired enzymologist who'd come to Harvard from Oxford and had been Boger's thesis advisor, "of giving away all we've got before we've got anything? I mean, yes, there are some splendid ideas here, and some superb people, and we will do it. But what's to stop boring old Glaxo [a British firm that had jumped from twenty-fifth to second among the world's drug companies on the strength of the world's best-selling drug, the antiulcer agent Zantac] from saying, 'Oh, oh, we see. Maybe we can do what you're telling us ourselves.' "

"But they *can't* do it, Jeremy," Boger interjected.

"But Merck can."

"No," Boger paused resolutely. "Merck can't either."

It had already become an article of faith at Vertex—as at most start-up companies—that large corporations were dinosaurs: too unadaptable and slow moving to compete at the forefront of research. But Knowles was not alone in suggesting that daring these companies to try might be an act of fatal arrogance, especially from a firm without a single hard scientific lead.

If there was a danger in Boger's intellect, Knowles knew this was

it. Boger was too smart and too competitive to ignore what he could learn from others. But because he was so certain of himself, he often underestimated them, turning against them with a haughty disdain. He especially liked to tweak the mighty. This had been the case when he and Kinsella spent months searching for a name for their new company and decided on Veritas. It was one thing for a fledgling business to draw on its contact with Harvard faculty members, another to appropriate the school's 350-year-old motto. More than most schools, Harvard anguished publicly about being involved with outside businesses. Knowles began receiving rueful, cautionary phone calls from senior administrators, including the university's legal counsel. Though Boger clearly relished Harvard's angst, Knowles quickly persuaded him of the "sensitivity, the horror, the absolute unacceptability" of Veritas, and the name was changed to Vertex.

Peculiarly, Vertex was at or near the apex of the science now being discussed in the lunchroom despite having done no experiments. In February, when Boger had considered what project to undertake first, his decision to improve on the experimental drug FK-506 had seemed prescient. Now, several developments had put Vertex at the center of one of the most promising areas in drug research.

Drugs are molecules. They attach themselves along critical points in the pathway of a disease. Since not all molecules are drugs, the difficulty, from a drugmaker's standpoint, is discovering those that are. There are other challenges. A drug molecule must be sufficiently unique to patent and must be capable of getting to its relevant target, another molecule within the toweringly complex molecular universe of the body. Raquel Welch, in the 1960s movie *The Fantastic Voyage*, discovered the extreme hazards of this. She and a miniaturized team of doctors undertook a harrowing repair mission inside the human body. Solubilized in an infinitesimal submarine, they tumbled through billowing plasma, dodged the clinging death grip of chainlike antibodies, and breached greasy cell walls to fix a remote area of the brain. The journey, lasting an hour, approximates the life cycle of at least one class of drugs—those delivered by injection into the bloodstream.