"Clone or Die"

If you know the question, you know half.

—Herb Boyer

Any sufficiently advanced technology is indistinguishable from magic.

—Arthur C. Clarke

Stan Cohen and Herb Boyer had also gone to Asilomar to debate the future of recombinant DNA. They found the conference irritating—even deflating. Boyer could not bear the infighting and the name-calling; he called the scientists "self-serving" and the meeting a "nightmare." Cohen refused to sign the Asilomar agreement (although as a grantee of the NIH, he would eventually have to comply with it).

Back in their own laboratories, they returned to an issue that they had neglected amid the commotion. In May 1974, Cohen's lab had published the "frog prince" experiment—the transfer of a frog gene into a bacterial cell. When asked by a colleague how he had identified the bacteria expressing the frog genes, Cohen had jokingly said that he had kissed the bacteria to check which ones would transform into a prince.

At first, the experiment had been an academic exercise; it had only turned biochemists' heads. (Joshua Lederberg, the Nobel Prize–winning biologist and Cohen's colleague at Stanford, was among the few who wrote, presciently, that the experiment "may completely change the pharmaceutical industry's approach to making biological elements, such as insulin and antibiotics.") But slowly, the media awoke to the potential impact of the study. In May, the *San Francisco Chronicle* ran a story on Cohen, focusing on the possibility that gene-modified bacteria might someday be used as biological "factories" for drugs or chemicals. Soon,

articles on gene-cloning technologies had appeared in *Newsweek* and the *New York Times*. Cohen also received a quick baptism on the seamy side of scientific journalism. Having spent an afternoon talking patiently to a newspaper reporter about recombinant DNA and bacterial gene transfer, he awoke the next morning to the hysterical headline: "Man-made Bugs Ravage the Earth."

At Stanford University's patent office, Niels Reimers, a savvy former engineer, read about Cohen and Boyer's work through these news outlets and was intrigued by its potential. Reimers—less patent officer and more talent scout—was active and aggressive: rather than waiting for inventors to bring him inventions, he scoured the scientific literature on his own for possible leads. Reimers approached Boyer and Cohen, urging them to file a joint patent on their work on gene cloning (Stanford and UCSF, their respective institutions, would also be part of that patent). Both Cohen and Boyer were surprised. During their experiments, they had not even broached the idea that recombinant DNA techniques could be "patentable," or that the technique could carry future commercial value. In the winter of 1974, still skeptical, but willing to humor Reimers, Cohen and Boyer filed a patent for recombinant DNA technology.

News of the gene-cloning patent filtered back to scientists. Kornberg and Berg were furious. Cohen and Boyer's claims "to commercial ownership of the techniques for cloning all possible DNAs, in all possible vectors, joined in all possible ways, in all possible organisms [is] dubious, presumptuous, and hubristic," Berg wrote. The patent would privatize the products of biological research that had been paid for with public money, they argued. Berg also worried that the recommendations of the Asilomar Conference could not be adequately policed and enforced in private companies. To Boyer and Cohen, however, all of this seemed much ado about nothing. Their "patent" on recombinant DNA was no more than a sheaf of paper making its way between legal offices—worth less, perhaps, than the ink that had been used to print it.

In the fall of 1975, with mounds of paperwork still moving through legal channels, Cohen and Boyer parted scientific ways. Their collaboration had been immensely productive—together they had published eleven landmark papers over five years—but their interests had begun to drift apart. Cohen became a consultant to a company called Cetus in California. Boyer returned to his lab in San Francisco to concentrate on his experiments on bacterial gene transfer.

In the winter of 1975, a twenty-eight-year-old venture capitalist, Robert Swanson, called Herb Boyer out of the blue to suggest a meeting. A connoisseur of popular-science magazines and sci-fi films, Swanson had also heard about a new technology called "recombinant DNA." Swanson had an instinct for technology; even though he knew barely any biology, he had sensed that recombinant DNA represented a tectonic shift in thinking about genes and heredity. He had dug up a dog-eared handbook from the Asilomar meeting, made a list of important players working on gene-cloning techniques, and had started working down the list alphabetically. *Berg* came before *Boyer*—but Berg, who had no patience for opportunistic entrepreneurs making cold calls to his lab, turned Swanson down. Swanson swallowed his pride and kept going down the list. B . . . Boyer was next. Would Boyer consider a meeting? Immersed in experiments, Herb Boyer fielded Swanson's phone call distractedly one morning. He offered ten minutes of his time on a Friday afternoon.

Swanson came to see Boyer in January 1976. The lab was located in the grimy innards of the Medical Sciences Building at UCSF. Swanson wore a dark suit and tie. Boyer appeared amid mounds of half-rotting bacterial plates and incubators in jeans and his trademark leather vest. Boyer knew little about Swanson—only that he was a venture capitalist looking to form a company around recombinant DNA. Had Boyer investigated further, he might have discovered that nearly all of Swanson's prior investments in fledgling ventures had failed. Swanson was out of work, living in a rent-shared apartment in San Francisco, driving a broken Datsun, and eating cold-cut sandwiches for lunch and dinner.

The assigned ten minutes grew into a marathon meeting. They walked to a neighborhood bar, talking about recombinant DNA and the future of biology. Swanson proposed starting a company that would use gene-cloning techniques to make medicines. Boyer was fascinated. His own son had been diagnosed with a potential growth disorder, and Boyer had been gripped by the possibility of producing human growth hormone, a protein to treat such growth defects. He knew that he might be able to make growth hormone in his lab by using his own method of stitching genes and inserting them into bacterial cells, but it would be useless: no sane person would inject his or her child with bacterial broth grown in a test tube in a science lab. To make a medical product, Boyer needed to

create a new kind of pharmaceutical company—one that would make medicines out of genes.

Three hours and three beers later, Swanson and Boyer had reached a tentative agreement. They would pitch in $500 each to cover legal fees to start such a company. Swanson wrote up a six-page plan. He approached his former employers, the venture firm Kleiner Perkins, for $500,000 in seed money. The firm took a quick look at the proposal and slashed that number fivefold to $100,000. ("This investment is highly speculative," Perkins later wrote apologetically to a California regulator, "but we are in the business of making highly speculative investments.")

Boyer and Swanson had nearly all the ingredients for a new company—except for a product and a name. The first potential product, at least, was obvious from the start: insulin. Despite many attempts to synthesize it using alternative methods, insulin was still being produced from mashed-up cow and pig innards, a pound of hormone from eight thousand pounds of pancreas—a near-medieval method that was inefficient, expensive, and outdated. If Boyer and Swanson could express insulin as a protein via gene manipulation in cells, it would be a landmark achievement for a new company. That left the issue of the name. Boyer rejected Swanson's suggestion of HerBob, which sounded like a hair salon on the Castro. In a flash of inspiration, Boyer suggested a condensation of Genetic Engineering Technology—Gen-en-tech.

Insulin: the Garbo of hormones. In 1869, a Berlin medical student, Paul Langerhans, had looked through a microscope at the pancreas, a fragile leaf of tissue tucked under the stomach, and discovered minute islands of distinct-looking cells studded across it. These cellular archipelagoes were later named the *islets of Langerhans*, but their function remained mysterious. Two decades later, two surgeons, Oskar Minkowski and Josef von Mering, had surgically removed the pancreas from a dog to identify the function of the organ. The dog was struck by an implacable thirst and began to urinate on the floor.

Mering and Minkowski were mystified: Why had removing an abdominal organ precipitated this odd syndrome? The clue emerged from a throwaway fact. A few days later, an assistant noted that the lab was buzzing with flies; they were swarming on the pools of dog urine that had now

congealed and turned sticky, like treacle.* When Mering and Minkowski tested the urine and the dog's blood, both were overflowing with sugar. The dog had become severely diabetic. Some factor synthesized in the pancreas, they realized, must regulate blood sugar, and its dysfunction must cause diabetes. The sugar-regulating factor was later found to be a hormone, a protein secreted into the blood by those "islet cells" that Langerhans had identified. The hormone was called isletin, and then insulin—literally, "island protein."

The identification of insulin in pancreatic tissue led to a race to purify it—but it took two further decades to isolate the protein from animals. Ultimately, in 1921, Banting and Best extracted a few micrograms of the substance out of dozens of pounds of cow pancreases. Injected into diabetic children, the hormone rapidly restored proper blood sugar levels and stopped their thirst and urination. But the hormone was notoriously difficult to work with: insoluble, heat-labile, temperamental, unstable, mysterious—insular. In 1953, after three more decades, Fred Sanger deduced the amino acid sequence of insulin. The protein, Sanger found, was made of two chains, one larger and one smaller, cross-linked by chemical bonds. U-shaped, like a tiny molecular hand, with clasped fingers and an opposing thumb, the protein was poised to turn the knobs and dials that so potently regulated sugar metabolism in the body.

Boyer's plan for the synthesis of insulin was almost comically simple. He did not have the gene for human insulin at hand—no one did—but he would build it from scratch using DNA chemistry, nucleotide by nucleotide, triplet upon triplet—ATG, CCC, TCC, and so forth, all the way from the first triplet code to the last. He would make one gene for the A chain, and another gene for the B chain. He would insert both the genes in bacteria and trick them into synthesizing the human proteins. He would purify the two protein chains and then stitch them chemically to obtain the U-shaped molecule. It was a child's plan. He would build the most ardently sought molecule in clinical medicine block by block, out of an Erector Set of DNA.

But even Boyer, adventurous as he was, blanched at lunging straight for insulin. He wanted an easier test case, a more pliant peak to scale before attempting the Everest of molecules. He focused on another protein—

* Minkowski does not recollect this, but others present in the lab have written about the urine-as-treacle experiment.

somatostatin—also a hormone, but with little commercial potential. Its main advantage was size. Insulin was a daunting fifty-one amino acids in length—twenty-one in one chain and thirty in the other. Somatostatin was its duller, shorter cousin, with just fourteen.

To synthesize the somatostatin gene from scratch, Boyer recruited two chemists from the City of Hope hospital in Los Angeles—Keiichi Itakura and Art Riggs—both veterans of DNA synthesis.* Swanson was bitterly opposed to the whole plan. Somatostatin, he feared, would turn into a distraction; he wanted Boyer to move to insulin directly. Genentech was living in borrowed space on borrowed money. Scratched even a millimeter below its surface, the "pharma company" was, in truth, a rented cubicle in an office space in San Francisco with an offshoot in a microbiology lab at UCSF, which, in turn, was about to subcontract two chemists at yet another lab to make genes—a pharmaceutical Ponzi scheme. Still, Boyer convinced Swanson to give somatostatin a chance. They hired an attorney, Tom Kiley, to negotiate the agreements among UCSF, Genentech, and the City of Hope. Kiley had never heard the term *molecular biology*, but felt confident because of his track record of representing unusual cases; before Genentech, his most famous former client had been Miss Nude America.

Time too felt borrowed at Genentech. Boyer and Swanson knew that two reigning wizards of genetics had also entered the race to make insulin. At Harvard, Walter Gilbert, the DNA chemist who would share the Nobel Prize with Berg and Sanger, was leading a formidable team of scientists to synthesize insulin using gene cloning. And at UCSF, in Boyer's own backyard, another team was racing toward the gene cloning. "I think it was on our minds most of the time . . . most days," one of Boyer's collaborators recalled. "I thought about it all the time: Are we going to hear an announcement that Gilbert has been successful?"

By the summer of 1977, working frantically under Boyer's anxious eye, Riggs and Itakura had assembled all the reagents for the synthesis of somatostatin. The gene fragments had been created and inserted into a bacterial plasmid. The bacteria had been transformed, grown, and prepped for the production of the protein. In June, Boyer and Swanson flew to Los Angeles to witness the final act. The team gathered in Riggs's lab in the

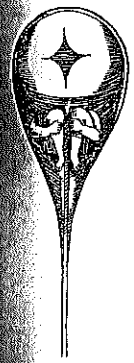
* They later added other collaborators, including Richard Scheller, from Caltech. Boyer put two researchers, Herbert Heyneker and Francisco Bolivar, on the project. The City of Hope added another DNA chemist, Roberto Crea.

morning. They leaned over to watch the molecular detectors check for the appearance of somatostatin in the bacteria. The counters blinked on, then off. Silence. Not even the faintest blip of a functional protein.

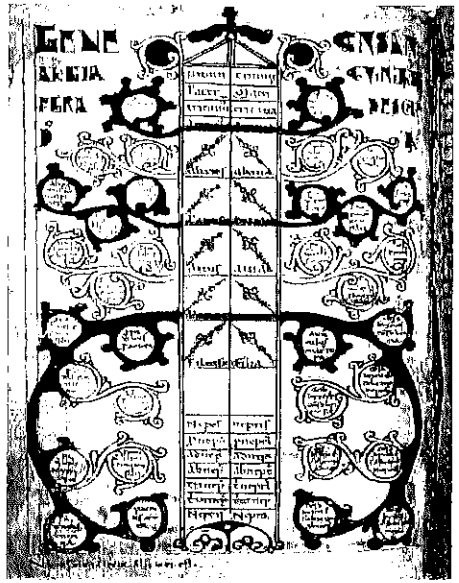
Swanson was devastated. The next morning, he developed acute indigestion and was sent to the emergency room. The scientists, meanwhile, recovered over coffee and doughnuts, poring through the experimental plan, troubleshooting. Boyer, who had worked with bacteria for decades, knew that microbes often digest their own proteins. Perhaps somatostatin had been destroyed by the bacteria—a microbe's last stand against being co-opted by human geneticists. The solution, he surmised, would be to add another trick to the bag of tricks: they would hook the somatostatin gene to another bacterial gene to make a conjoined protein, then cleave off the somatostatin after. It was a genetic bait and switch: the bacteria would think they were making a bacterial protein, but would end up (secretly) secreting a human one.

It took another three months to assemble the decoy gene, with somatostatin now Trojan-horsed within another bacterial gene. In August 1977, the team reassembled at Riggs's lab for the second time. Swanson nervously watched the monitors flicker on, and momentarily turned his face away. The detectors for the protein crackled again in the background. As Itakura recalled, "We have about ten, maybe fifteen samples. Then we look at the printout of the radioimmunoassay, and the printout show[s] clearly that the gene is expressed." He turned to Swanson. "Somatostatin is there."

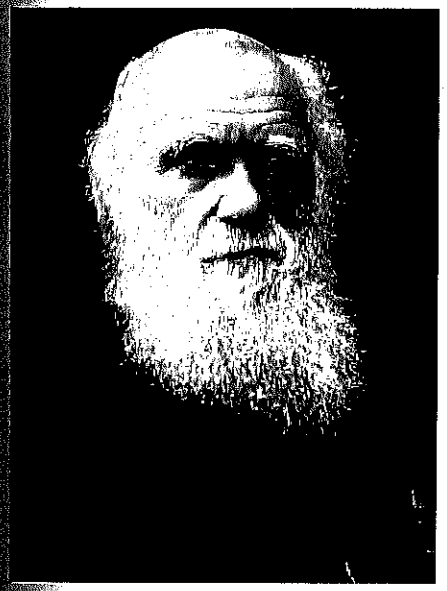
Genentech's scientists could barely stop to celebrate the success of the somatostatin experiment. One evening, one new human protein; by the next morning, the scientists had regrouped and made plans to attack insulin. The competition was fierce, and rumors abounded: Gilbert's team had apparently cloned the native human gene out of human cells and were readying to make the protein in buckets. Or the UCSF competitors had synthesized a few micrograms of protein and were planning to inject the human hormone into patients. Perhaps somatostatin *had* been a distraction. Swanson and Boyer suspected ruefully that they had taken a wrong turn and been left behind in the insulin race. Dyspeptic even during the best of times, Swanson edged toward another bout of anxiety and indigestion.

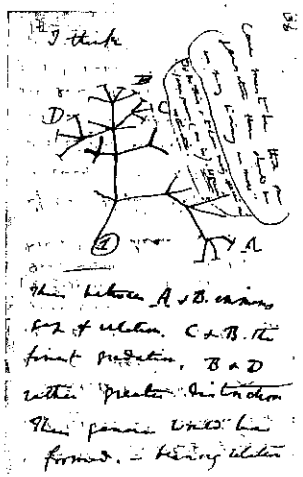


This homunculus, wrapped inside human sperm, was drawn by Nicolaas Hartsoeker in 1694. Like many other biologists in his time, Hartsoeker believed in "spermism," the theory that the information to create a fetus was transmitted by the miniature human form lodged inside sperm.



In medieval Europe, "trees of lineage" were often created to mark the ancestors and descendants of noble families. These trees were used to stake claims on peerage and property, or to seek marital arrangements between families (in part, to decrease the chances of consanguineous marriages between cousins). The word *gene*—at the top left corner—was used in the sense of genealogy or descent. The modern connotation of *gene*, as a unit of hereditary information, appeared centuries later in 1909.





Charles Darwin (here in his seventies) and his "tree of life" sketch, showing organisms radiating out from a common ancestral organism (with the doubt-ridden phrase "I think," scribbled above the diagram). Darwin's theory of evolution by variation and natural selection demanded a theory of heredity via genes. Close readers of Darwin's theory realized that evolution could work only if there were indivisible, but mutable, particles of heredity that transmit information between parents and offspring. Yet Darwin, having never read Gregor Mendel's paper, never found an adequate formulation of such a theory during his lifetime.

Even without subtle techniques to alter human genomes, the capacity to assess a child's genome *in utero* has led to vast dysgenic efforts around the world. In parts of China and India, the assessment of male versus female gender by amniocentesis, and the selective abortion of female fetuses, has skewed the sex ratio to 0.8 females to 1 male and caused unprecedented alterations of population and family structures.

Faster and more accurate gene-sequencing machines (housed inside gray boxlike containers) linked to supercomputers that analyze and annotate genetic information can now sequence individual human genomes in months. Variations of this technique can be used to sequence the genome of a multicelled embryo or a fetus, enabling preimplantation genetic diagnosis and *in utero* diagnosis of future illness.

Jennifer Doudna (*right*), a biologist and RNA researcher at Berkeley, is among those working on a system to deliver targeted, intentional mutations in genes. In principle, the system can be used to "edit" the human genome, although the technology still remains to be perfected and assessed for safety and fidelity. If intentional genetic changes were introduced into sperm, egg, or human embryonic stem cells, the technology would portend the genesis of humans with altered genes.

Ironically, it was Asilomar—the very meeting that Boyer had so vociferously disparaged—that came to their rescue. Like most university laboratories with federal funding, Gilbert's lab at Harvard was bound by the Asilomar restrictions on recombinant DNA. The restrictions were especially severe because Gilbert was trying to isolate the "natural" human gene and clone it into bacterial cells. In contrast, Riggs and Itakura, following the lead with somatostatin, had decided to use a chemically synthesized version of the insulin gene, building it up nucleotide by nucleotide from scratch. A synthetic gene—DNA created as a naked chemical—fell into the gray zone of Asilomar's language and was relatively exempt. Genentech, as a privately funded company, was also relatively exempt from the federal guidelines.* The combination of factors proved to be a crucial advantage for the company. As one worker recalled, "Gilbert was, as he had for many days past, trudging through an airlock, dipping his shoes in formaldehyde on his way into the chamber in which he was obliged to conduct his experiments. Out at Genentech, we were simply synthesizing DNA and throwing it into bacteria, none of which even required compliance with the NIH guidelines." In the world of post-Asilomar genetics, "being natural" had turned out to be a liability.

Genentech's "office"—the glorified booth in San Francisco—was no longer adequate. Swanson began scouring the city for lab space for his nascent company. In the spring of 1978, having searched up and down the Bay Area, he found a suitable site. Stretched across a tawny, sun-scorched flank of hillside a few miles south of San Francisco, the place was called Industrial City, although it was hardly industrial and barely a city. Genentech's lab was ten thousand square feet of a raw warehouse on 460 Point San Bruno Boulevard, set amid storage silos, dump sites, and airport-freight hangars. The back half of the warehouse housed a storage facility

* Genentech's strategy for the synthesis of insulin was also critical to its relative exemption from Asilomar's protocols. In the human pancreas, insulin is normally synthesized as a single contiguous protein and then cut into two pieces, leaving just a narrow cross-linkage. Genentech, in contrast, had chosen to synthesize the two chains of insulin, A and B, as separate, individual proteins and link them together afterward. Since the two separate chains used by Genentech were not "natural" genes, the synthesis did not fall under the federal moratorium that restricted the creation of recombinant DNA with "natural" genes.

for a distributor of porn videos. "You'd go through the back of Genentech's door and there would be all these movies on shelves," one early recruit wrote. Boyer hired a few additional scientists—some barely out of graduate school—and began to install equipment. Walls were constructed to divide the vast space. A makeshift lab was created by slinging black tarp across part of the roof. The first "fermenter" to grow gallons of microbial sludge—an upscale beer vat—arrived that year. David Goeddel, the company's third employee, walked around the warehouse in sneakers and a black T-shirt that read CLONE OR DIE.

Yet no human insulin was in sight. In Boston, Swanson knew, Gilbert had upped his war effort—literally. Fed up with the constraints on recombinant DNA at Harvard (on the streets of Cambridge, young protesters were carrying placards against gene cloning), Gilbert had gained access to a high-security biological-warfare facility in England and dispatched a team of his best scientists there. The conditions in the military facility were absurdly stringent. "You totally change your clothes, shower in, shower out, have gas masks available so that if the alarm goes off you can sterilize the entire laboratory," Gilbert recalled. The UCSF team, in turn, sent a student to a pharmaceutical lab in Strasbourg, France, hoping to create insulin at the well-secured French facility.

Gilbert's group oscillated at the brink of success. In the summer of 1978, Boyer learned that Gilbert's team was about to announce the successful isolation of the human insulin gene. Swanson braced himself for another breakdown—his third. To his immense relief, the gene that Gilbert had cloned was not human but *rat* insulin—a contaminant that had somehow tainted the carefully sterilized cloning equipment. Cloning had made it easy to cross the barriers between species—but that same breach meant that a gene from one species could contaminate another in a biochemical reaction.

In the narrow cleft of time between Gilbert's move to England and the mistaken cloning of rat insulin, Genentech forged ahead. It was an inverted fable: an academic Goliath versus a pharmaceutical David, one lumbering, powerful, handicapped by size, the other nimble, quick, adept at dancing around rules. By May 1978, the Genentech team had synthesized the two chains of insulin in bacteria. By July, the scientists had purified the proteins out of the bacteria debris. In early August, they snipped off the attached bacterial proteins and isolated the two individual chains. Late at night on August 21, 1978, Goeddel joined the protein

chains together in a test tube to create the first molecules of recombinant insulin.

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In September 1978, two weeks after Goeddel had created insulin in a test tube, Genentech applied for a patent for insulin. Right at the onset, the company faced a series of unprecedented legal challenges. Since 1952, the United States Patent Act had specified that patents could be issued on four distinct categories of inventions: methods, machines, manufactured materials, and compositions of matter—the "four M's," as lawyers liked to call the categories. But how could insulin be pigeonholed into that list? It was a "manufactured material," but virtually every human body could evidently manufacture it without Genentech's ministrations. It was a "composition of matter," but also, indisputably, a natural product. Why was patenting insulin, the protein or its gene, different from patenting any other part of the human body—say, the nose or cholesterol?

Genentech's approach to this problem was both ingenious and counterintuitive. Rather than patenting insulin as "matter" or "manufacture," it concentrated its efforts, boldly, on a variation of "method." Its application claimed a patent for a "DNA vehicle" to carry a gene into a bacterial cell, and thereby produce a recombinant protein in a microorganism. The claim was so novel—no one had ever produced a recombinant human protein in a cell for medicinal use—that the audacity paid off. On October 26, 1982, the US Patent and Trademark Office (USPTO) issued a patent to Genentech to use recombinant DNA to produce a protein such as insulin or somatostatin in a microbial organism. As one observer wrote: "effectively, the patent claimed, as an invention, [all] genetically modified microorganisms." The Genentech patent would soon become one of the most lucrative, and most hotly disputed, patents in the history of technology.

Φ

Insulin was a major milestone for the biotechnology industry, and a blockbuster drug for Genentech. But it was not, notably, the medicine that would catapult gene-cloning technology to the forefront of public imagination.

In April 1982, a ballet dancer in San Francisco, Ken Horne, visited a dermatologist, complaining of an inexplicable cluster of symptoms. Horne had felt weak for months and developed a cough. He had bouts of intractable diarrhea, and weight loss had hollowed his cheeks and made his neck muscles stand out like leather straps. His lymph nodes had swollen. And now—he pulled his shirt up to demonstrate—reticulated bumps were emerging on his skin, purple-blue of all colors, like hives in a macabre cartoon film.

Horne's case was not isolated. Between May and August 1982, as the coasts sweltered in a heat wave, similarly bizarre medical cases were reported in San Francisco, New York, and Los Angeles. At the CDC in Atlanta, a technician was asked to fill nine requests for pentamidine, an unusual antibiotic reserved to treat *Pneumocystis* pneumonia. These requisitions made no sense: PCP was a rare infection that typically afflicted cancer patients with severely depleted immune systems. But these applications were for young men, previously in excellent health, whose immune systems had suddenly been pitched into inexplicable, catastrophic collapse.

Horne, meanwhile, was diagnosed with Kaposi's sarcoma—an indolent skin tumor found among old men in the Mediterranean. But Horne's case, and the other nine cases reported in the next four months, bore little resemblance to the slow-growing tumors previously described as Kaposi's in the scientific literature. These were fulminant, aggressive cancers that spread rapidly through the skin and into the lungs, and they seemed to have a predilection for gay men living in New York and San Francisco. Horne's case mystified medical specialists, for now, as if to intersect puzzle upon puzzle, he developed *Pneumocystis* pneumonia and meningitis as well. By late August, an epidemiological disaster was clearly appearing out of thin air. Noting the preponderance of gay men afflicted, doctors began to call it GRID—gay-related immune deficiency. Many newspapers accusingly termed it the "gay plague."

By September, the fallacy of that name had become evident: symptoms of immunological collapse, including *Pneumocystis* pneumonia and strange variants of meningitis, had now begun to sprout up among three patients with hemophilia A. Hemophilia, recall, was the bleeding illness of the English royals—caused by a single mutation in the gene for a crucial clotting factor in blood, called factor VIII. For centuries, patients with hemophilia had lived in constant fear of a bleeding crisis: a nick in the skin could snowball into disaster. By the mid-1970s, though, hemo-

philiacs were being treated with injections of concentrated factor VIII. Distilled out of thousands of liters of human blood, a single dose of the clotting factor was equivalent to a hundred blood transfusions. A typical patient with hemophilia was thus exposed to the condensed essence of blood from thousands of donors. The emergence of the mysterious immunological collapse among patients with multiple blood transfusions pinpointed the cause of the illness to a blood-borne factor that had contaminated the supply of factor VIII—possibly a novel virus. The syndrome was renamed acquired immunodeficiency syndrome—AIDS.

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In the spring of 1983, against the backdrop of the early AIDS cases, Dave Goeddel at Genentech began to focus on cloning the factor VIII gene. As with insulin, the logic behind the cloning effort was immediately evident: rather than purifying the missing clotting factor out of liters of human blood, why not create the protein artificially, using gene cloning? If factor VIII could be produced through gene-cloning methods, it would be virtually free of any human contaminants, thereby rendering it inherently safer than any blood-derived protein. Waves of infections and deaths might be prevented among hemophiliacs. It was Goeddel's old T-shirt slogan brought to life—"clone or die."

Goeddel and Boyer were not the only geneticists musing about cloning factor VIII. As with the cloning of insulin, the effort had evolved into a race, although with different competitors. In Cambridge, Massachusetts, a team of researchers from Harvard, led by Tom Maniatis and Mark Ptashne, were also racing toward the factor VIII gene, having formed their own company, named the Genetics Institute—colloquially called GI. The factor VIII project, both teams knew, would challenge the outer limits of gene-cloning technology. Somatostatin had 14 amino acids; insulin had 51. Factor VIII had 2,350. The leap in size between somatostatin and factor VIII was 160-fold—almost equivalent to the jump in distance between Wilbur Wright's first airborne circle at Kitty Hawk and Lindbergh's journey across the Atlantic.

The leap in size was not just a quantitative barrier; to succeed, the gene cloners would need to use new cloning technologies. Both the somatostatin and insulin genes had been created from scratch by stitching together bases of DNA—A added chemically to the G and the C and so forth. But

the factor VIII gene was far too large to be created using DNA chemistry. To isolate the factor VIII gene, both Genentech and GI would need to pull the native gene out of human cells, spooling it out as if extracting a worm from the soil.

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But the "worm" would not come out easily, or intact, from the genome. Most genes in the human genome are, recall, interrupted by stretches of DNA called introns, which are like garbled stuffers placed in between parts of a message. Rather than the word *genome*, the actual gene reads *gen . . . . . om . . . . . e*. The introns in human genes are often enormous, stretching across vast lengths of DNA, making it virtually impossible to clone a gene directly (the intron-containing gene is too long to fit into a bacterial plasmid).

Maniatis found an ingenious solution: he had pioneered the technology to build genes out of RNA templates using reverse transcriptase, the enzyme that could build DNA from RNA. The use of reverse transcriptase made gene cloning vastly more efficient. Reverse transcriptase made it possible to clone a gene *after* the intervening stuffer sequences had been snipped off by the cell's splicing apparatus. The cell would do all the work; even long, unwieldy, intron-interrupted genes such as factor VIII would be processed by the cell's gene-splicing apparatus and could thus be cloned from cells.

By the late summer of 1983, using all the available technologies, both teams had managed to clone the factor VIII gene. It was now a furious race to the finish. In December 1983, still running shoulder to shoulder, both groups announced that they had assembled the entire sequence and inserted the gene into a plasmid. The plasmid was then introduced into hamster-derived ovary cells known for their ability to synthesize vast quantities of proteins. In January 1984, the first cargoes of factor VIII began to appear in the tissue-culture fluid. In April, exactly two years after the first AIDS clusters had been reported in America, both Genentech and GI announced that they had purified recombinant factor VIII in test tubes—a blood-clotting factor untainted by human blood.

In March 1987, Gilbert White, a hematologist, conducted the first clinical trial of the hamster-cell-derived recombinant factor VIII at the Center for Thrombosis in North Carolina. The first patient to be treated was

G.M., a forty-three-year-old man with hemophilia. As the initial drops of intravenous liquid dripped into his veins, White hovered anxiously around G.M.'s bed, trying to anticipate reactions to the drug. A few minutes into the transfusion, G.M. stopped speaking. His eyes were closed; his chin rested on his chest. "Talk to me," White urged. There was no response. White was about to issue a medical alert when G.M. turned around, made the sound of a hamster, and burst into laughter.

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News of G.M.'s successful treatment spread through a desperate community of hemophiliacs. AIDS among hemophiliacs had been a cataclysm within a cataclysm. Unlike gay men, who had quickly organized a concerted, defiant response to the epidemic—boycotting bathhouses and clubs, advocating safe sex, and campaigning for condoms—hemophiliacs had watched the shadow of the illness advance with numb horror: they could hardly boycott blood. Between April 1984 and March 1985, until the first test for virally contaminated blood was released by the FDA, every hemophiliac patient admitted to a hospital faced the terrifying choice of bleeding to death or becoming infected with a fatal virus. The infection rate among hemophiliacs during this period was staggering: among those with the severe variant of the disease, 90 percent would acquire HIV through contaminated blood.

Recombinant factor VIII arrived too late to save the lives of most of these men and women. Nearly all the HIV-infected hemophiliacs from the initial cohort would die of the complications of AIDS. Even so, the production of factor VIII from its gene broke important conceptual ground—although it was tinged with peculiar irony. The fears of Asilomar had been perfectly inverted. In the end, a "natural" pathogen had unleashed havoc on human populations. And the strange artifice of gene cloning—inserting human genes into bacteria and then manufacturing proteins in hamster cells—had emerged as potentially the safest way to produce a medical product for human use.

◐

It is tempting to write the history of technology through products: the wheel; the microscope; the airplane; the Internet. But it is more illumi-

nating to write the history of technology through transitions: linear motion to circular motion; visual space to subvisual space; motion on land to motion in air; physical connectivity to virtual connectivity.

The production of proteins from recombinant DNA represented one such crucial transition in the history of medical technology. To understand the impact of this transition—from gene to medicine—we need to understand the history of medicinal chemicals. Stripped to its bare essence, a medicinal chemical—a drug—is nothing more than a molecule that enables a therapeutic change in human physiology. Medicines can be simple chemicals—water, in the right context and at the right dose, is a potent drug—or they can be complex, multidimensional, many-faced molecules. They are also astoundingly rare. Although there are seemingly thousands of drugs in human usage—aspirin alone comes in dozens of variants—the number of molecular *reactions* targeted by these drugs is a minuscule fraction of the total number of reactions. Of the several million variants of biological molecules in the human body (enzymes, receptors, hormones—and so forth), only about 250—0.025 percent—are therapeutically modulated by our current pharmacopeia. If human physiology is visualized as a vast global telephone network with interacting nodes and networks, then our current medicinal chemistry touches only a fraction of a fraction of its complexity; medicinal chemistry is a pole operator in Wichita tinkering with a few lines in the network's corner.

The paucity of medicines has one principal reason: specificity. Nearly every drug works by binding to its target and enabling or disabling it—turning molecular switches on or off. To be useful, a drug must bind to its switches—but to only a selected set of switches; an indiscriminate drug is no different from a poison. Most molecules can barely achieve this level of discrimination—but proteins have been designed explicitly for this purpose. Proteins, recall, are the hubs of the biological world. They are the enablers and the disablers, the machinators, the regulators, the gatekeepers, the operators, of cellular reactions. They *are* the switches that most drugs seek to turn on and off.

Proteins are thus poised to be some of the most potent and most discriminating medicines in the pharmacological world. But to make a protein, one needs its gene—and here recombinant DNA technology provided the crucial missing stepping-stone. The cloning of human genes allowed scientists to manufacture proteins—and the synthesis of proteins opened the possibility of targeting the millions of biochemical reactions

in the human body. Proteins made it possible for chemists to intervene on previously impenetrable aspects of our physiology. The use of recombinant DNA to produce proteins thus marked a transition not just between one gene and one medicine, but between genes and a novel universe of drugs.

Φ

On October 14, 1980, Genentech sold 1 million of its shares to the public, provocatively listing itself at the stock exchange under the trading symbol GENE. This initial sale would rank among the most dazzling debuts of any technology company in Wall Street history: within a few hours, the company had generated $35 million in capital. By then, the pharmaceutical giant Eli Lilly had acquired the license to produce and sell recombinant insulin—called *Humulin*, to distinguish it from cow and pig insulin—and was rapidly expanding its market. Sales rose from $8 million in 1983 to $90 million in 1996 to $700 million in 1998. Swanson—"a short, chunky chipmunk-cheeked thirty-six-year-old," as *Esquire* magazine described him—was now a millionaire several times over, as was Boyer. A graduate student who had held on to a few throwaway shares for helping to clone the somatostatin gene over the summer of 1977 woke up one morning and found himself a newly minted multimillionaire.

In 1982, Genentech began to produce human growth hormone—HGH—used to treat certain variants of dwarfism. In 1986, biologists at the company cloned alpha interferon, a potent immunological protein used to treat blood cancers. In 1987, Genentech made recombinant TPA, a blood thinner to dissolve the clots that occur during a stroke or a heart attack. In 1990, it launched efforts to create vaccines out of recombinant genes, beginning with a vaccine against hepatitis B. In December 1990, Roche Pharmaceuticals acquired a majority stake in Genentech for $2.1 billion. Swanson stepped down as the chief executive; Boyer left his position as vice president in 1991.

In the summer of 2001, Genentech launched its physical expansion into the largest biotech research complex in the world—a multiacre stretch of glass-wrapped buildings, rolling greens, and Frisbee-playing research students that is virtually indistinguishable from any university campus. At the center of the vast complex sits a modest bronze statue of a man in a suit gesticulating over a table to a scientist in flared jeans and

a leather vest. The man is leaning forward. The geneticist looks puzzled and is gazing distantly over the man's shoulder.

Swanson, unfortunately, was not present for the formal unveiling of the statue commemorating his first meeting with Boyer. In 1999, at age fifty-two, he was diagnosed with glioblastoma multiforme, a brain tumor. He died on December 6, 1999, at home in Hillsborough, a few miles from Genentech's campus.

PART FOUR

"THE PROPER STUDY OF MANKIND IS MAN"

Human Genetics (1970–2005)