Just Jim

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SAVED BY THE DOUBLE HELIX

In 1962, as a ninth grader, I was in a program for the scientifically gifted. One day, responding to an after-class question, my teacher whispered, lest anyone overhear, that every cell of the body had a complete blueprint for the entire organism. Ridiculous, I thought. First, how could anyone know this to be true? Second, even if it were true, how foolish to burden every cell with all this information. How could the specialized cell know which part of the blueprint it was meant to read? Third, such a blueprint could never be embodied, let alone copied or read.

A strong prejudice formed on the spot: Life was a freakish accident on the planet earth, and no good principles would come by studying it. If the workings of life were a mystery, it was because its designs were so utterly silly that they could not be disentangled through the efforts of rational minds. I vowed that I would waste no more time on Biology.

By the time I had entered twelfth grade, my interest in Physics suffered a similar fate. At the atomic level, the rules of the universe became increasingly capricious, and beyond a certain scale, the rules themselves were forever veiled. Since humans held no interest for me, as any species capable of the death camps and Hiroshima could hardly be worth study, by a process of deduction all that remained was Mathematics. Poetry was to be found there, embedded in design and economy of thought, and its only limits were imagination and the power of mind.

Two years into Princeton, limited by both my imagination and power of mind, and lacking sustaining human relationships, my cognitive world had crumbled, followed soon after by my emotional state. Or perhaps it was the reverse sequence. From that cognitive and emotional rubble, I began a long period of reconstruction. This recovery drew strength from family and friends and from some surprising quarters, including a textbook on molecular biology.

The first step was to recognize that if I were in an existential hell, so was everyone else. This reconciled me to humanity, and one of my early decisions was to help others, should I achieve competence. Pursuit of Medicine seemed logical. Of course, the high life of the mind was no longer an option, and I would have to study Biology.

J.T. Bonner and Edward Cox taught Biology 101, 102. The suggested reading for the first semester included D'Arcy Thompson's *On Growth and Form* (Thompson 1942).

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Cold Spring Harbor changes people. From promising to fully fledged, wide-eyed to worldly, and, sometimes, from sensitive to cynical. And these changes can happen rapidly, within the span of a postdoctoral fellowship or even over a summer or two. But Mike Wigler has worked at Cold Spring Harbor for 25 years and has changed imperceptibly, if at all. As he describes in the following essay, all of the adjustments needed to succeed in the Cold Spring Harbor style of science were already in place before he came to the Laboratory. So well-bonded was Wigler to Watsonian laws of behavior and thought that the CSHL created by Jim may be the only place where Wigler's science could have flourished so abundantly.

In 1981, Mike's lab was among the first to isolate the human *ras* oncogene. Two years later, his laboratory identified a form of the gene in yeast, providing a powerful model system to map the *ras* signaling pathway from cell surface to the nucleus. A vivid, if starry-eyed, account of these experiments was published in *Natural Obsessions: The Search for the Oncogene* by Natalie Angier (1988, Houghton Mifflin, Boston).

To discover new cancer genes, Mike, in collaboration with Nikolai Lisitsyn, developed a powerful technique called representational difference analysis (RDA), which detects genetic abnormalities that accumulate in the genomes of tumor cells, including DNA amplifications, rearrangements, loss of heterozygosity, and homozygous deletions. RDA led Mike to the *PTEN* gene, a tumor suppressor gene that is mutated in many kinds of human tumors and in the germ lines of people who inherit a condition (Cowden's syndrome) that predisposes them to breast, thyroid, and other cancers.

More recently, Mike has begun to combine representational approaches of genomic analysis with DNA microarray technology to develop methods for high-resolution scanning of the genomes of cancer cells.

This seemed a heroic but unsuccessful effort to infuse Biology with Science. *The Double Helix* by James Watson was also suggested reading (Watson 1968). This, on the other hand, was an adventure story of the highest order. A brash American had made the biological discovery of the century. Armed with a sharp instinct for significance, an unrelentingly honest eye, and blindness for barriers, Watson had revealed the Great Secret before hardly anyone knew it existed. To carry off the crime, this Hermes needed an Hephaestus, Francis Crick, the accomplice whose wayward genius could be diverted for sufficient moments.

I have always been able to block out the world, and I had the barest awareness of DNA before reading *The Double Helix*. I knew none of the details. My awareness of molecular biology came upon first reading. *The Double Helix* was for me an historical record, a morality play, a great scientific treatise, and an adventure story all at once. It made a deeper impression on me than anything I had read before or since, with the exception of Aesop's Fables (from my early boyhood), the Bible, and Kafka's *The Castle*. The horizons of the possible reopened. The world was not bleak. I just had taken the wrong view.

All this was confirmed in the second semester. The text was the second edition of Watson's *Molecular Biology of the Gene* (Watson 1970). This brave melding of new ideas

from chemistry, techniques from physics, and logical reasoning gave proof that a new science had been born. I flew through the pages. The biological "world" was presented as the problems Nature had overcome, with problems in abundance. The laws of physics were the tools Nature used to create herself. Perceiving her problems and her solutions was the human challenge, testing our imagination, resourcefulness, and knowledge of the laws. Each discovery was an adventure story, judged by its relevance to the other stories and by how well it was told.

I took joy that the world had opened, but I was to miss the fun. I was not to partake. My fate was Medical School, my penance for years of closed-minded thinking.

PRELUDE TO A MEETING

No one accepts penance well, especially self-administered, and I never made it through medical school. At the time, there was an irrepressible excitement for all of the biological sciences. Drawn to this excitement in my first year at Rutgers Medical School, I began to experiment, something I had never done before. I discovered, if only for myself, that disrupting the cytoskeleton could inhibit replication of certain viruses and that I could culture nerve cells from the embryonic chick heart. Everywhere I turned I recognized unexplored terrain. But before long, the medical deans at Columbia University, to which I had transferred, discovered something too, that I had been an admissions error.

I made the transition from medical school to graduate school smoothly, completed my graduate work with Bernie Weinstein on tumor promoters, and commenced my work with Richard Axel and Saul Silverstein on gene transfer. But I had neglected to write my thesis and was unable to afford dates with my girlfriend. I woke up, wrote my thesis, and graduated. Suddenly I was a hot property in the job market.

Never having lived more than 40 miles from New York City, I wanted to stay in the area. My family was on Long Island, and my girlfriend lived in Manhattan. Mike Botchan, a friend of Axel and a scientist at Cold Spring Harbor Laboratory, knew and appreciated my work. Mike had done beautiful work, as had other scientists at the Lab, producing discoveries that had the same flavor and rigor as those described in the *Molecular Biology of the Gene*. I recognized the signature. Mike encouraged me to give a seminar at the Lab and meet Jim Watson. But Columbia was also interested in keeping me.

There was no love lost between Columbia and Jim Watson. Columbia was home to Erwin Chargaff, the nucleic acid chemist who discovered the parity rule: the content of G matched that of C, and A of T, in DNA. This was a huge clue to the puzzle, explained by the complementarity of the double helix. Apparently, Chargaff held a grudge. Even in 1974, when I took the required course in biochemistry, one of his colleagues would give one lecture questioning whether the model of the double helix was scientifically sound.

I inferred that an unintended side effect of publishing *The Double Helix*, and the style of science that it spawned, was to radically change the equilibrium between thought, data, and belief. It is undeniable that the results of molecular biologists had *appeal*. The unstated fear of the old guard was the wall that separated what we believed to be true from what we wished to be true would erode. This wall, mortared

over centuries with blood, was what made Science strong. I thought that molecular biology was rigorous, but the established forces were very resistant, and as a result, Columbia had remained at the station, very much after the train had departed.

To regain lost momentum, Columbia had hired Sol Spiegelman to direct an Institute for Cancer Research. The Institute was in effect a ghetto for molecular biologists at the College of Physicians & Surgeons, segregated geographically at the Delafield Hospital along Riverside Drive. I viewed it as an oasis, removed from the plodding habits of established scientific thinking.

Sol had established the first practical method of using hybridization to distinguish different nucleic acid species (filter hybridization) and had established the first in vitro self-replicating system, based on RNA phage polymerases and templates, a precursor to the polymerase chain reaction and in vitro evolution. He was an excellent biochemist and had missed by a few months being the first to discover reverse transcriptase.

Sol clearly had great respect for Jim Watson, and the students who had been through Jim's lab at Harvard. But what I think Sol most admired about Jim was that he kept his name off the papers of his students. Don Mills told me this Spiegelman story. One morning, when Don was a lowly technician in Sol's lab, he had an idea for an experiment, which he communicated to a postdoc. This postdoc apparently talked to Sol. Later that afternoon, Sol came to Don and said, "I had a great idea. Try this..."

Despite the almost universal admiration for what Jim Watson had accomplished, charges and innuendos began to flow from many quarters. Jim was prone to uncritical enthusiasms. He was a finisher, not an originator. He set researcher against researcher in an intramural competition to increase productivity. He was obsessed with sex. He had a horribly nasty streak. And maybe he was an anti-Semite.

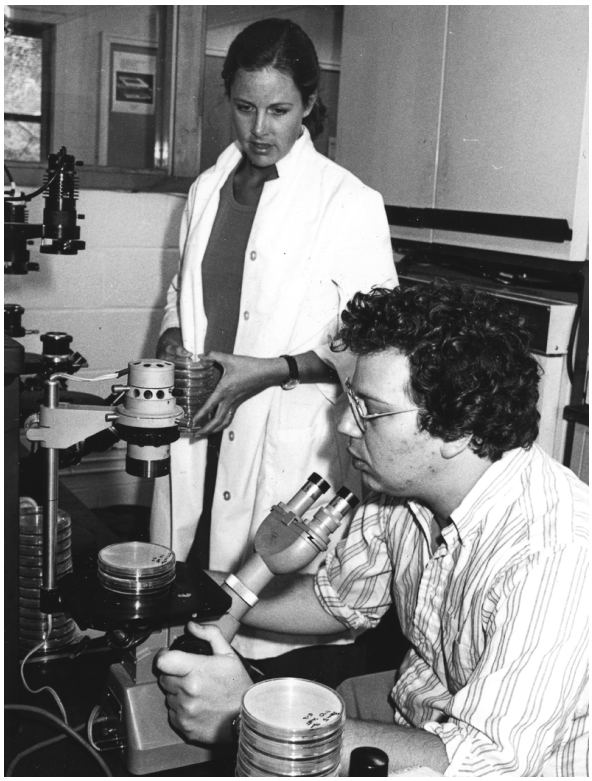
Of course, none of this was true. But even Botchan, who was exceedingly fond of Jim, set a cautionary note. When I talk to Jim, Botchan suggested, I might not be able to understand him; he mumbles and is often incoherent.

JUST JIM

I did come to Cold Spring Harbor, and sank into my work, which is all I had ever wanted to do. Jim and Liz came to our wedding, and my wife Deedee and I still have the pitcher with the painted pig they gave us as a wedding gift.

Jim did harshly criticize my job seminar, but only after I had been at the Lab for 20 years. His faith was in bright and ambitious young people, and his job was to identify them and stoke their ambitions. From the beginning, Jim supported my work and my ego, unstintingly. I never saw him treat any other scientist differently, or set one against another. Doing science is hard enough. His advice was unerring when from time to time I came to him with the choices that I could not make. When I ran over budget, which I did every year except one, Jim never tried to trim my sails. You have to spend money to bring in money, he explained. Think big. "A Director's job," he once told me, "is to say yes. If I have to say no, then I have failed."

I did find his conversations hard to follow at first, as he leapt from observation to observation, and he did tend to mumble. With time it made more sense, as I did the work to find the thread. There was always a thread, often an interesting and enter-



Celia Frazer and Mike Wigler, 1979. (Courtesy CSHL Archives.)

taining observation about human social organization, or a concealed piece of advice. But I never gave Jim much to work with and never shared Jim's fascination with the blue bloods of Long Island's Gold Coast. ("Always have rich friends," he advised.) After many years, Jim learned that I wasn't a conversationalist. So now he talks to me mainly about tennis, a shared passion. Jim wishes it remembered, he bragged, that at age 75 he could serve at 100 mph.

I never experienced, nor saw, the famous bad temper, except once. It was in a dispute with Columbia over patent rights. Jim could use his anger effectively in a negotiation, and his reputation as a hothead served him well. He explained to me that you have to be judicious when calling someone a "shit," or especially a "little shit." Reserve that for special occasions, he advised.

Jim was often outspoken, though, and this landed him in hot water more than once, most notably when he went to work for the NIH as the first Director of the Human Genome Project. I was very disappointed that he took that assignment—that a great man of science had joined the bureaucracy in Washington. So when I heard the news that he was fired, I was delighted. He had not capitulated.

On that day, as I saw Jim cross the lawn in front of Grace Auditorium, I went up to him to offer my congratulations. For the first time, Jim glared hard at me. Perhaps he misinterpreted my unrestrained joy as schadenfreude. Grimacing, he told me, "This is the worst day of my life."

PRECURSORS

How had I so misunderstood him? This puzzled me for years, until I read a biography of Niels Bohr by Abraham Pais (1991). Niels Bohr was the Danish physicist who at a very young age proposed the first quantum structure of the atom. He was beloved by the Danes, who regarded him as a national treasure and hero. Bohr was the Director of the renowned Institute of Theoretical Physics, where many of the great physicists of the twentieth century were mentored. He was always generous with advice, and his enthusiasm for science irrepressible. And here is a critical detail. Bohr mumbled, and leapt from subject to subject in an apparently unordered manner, so much so that conversations with him were invariably described as difficult to follow. Bohr, later in life, became involved in politics and the role of physics in modern society.

The parallels were unmistakable. Then I recalled from my reading of *The Double Helix* that Jim had spent a brief period as a postdoctoral fellow at Bohr's Institute and had dinner with the great man. This was before Jim's place in History had been secured, and surely Bohr must have profoundly influenced him, perhaps subconsciously.

Like Bohr, Jim viewed himself, and came to be viewed, as a citizen-scientist. He always had an eye for the larger epic, and eagerly moved in a much larger circle of life. He suffered miserably under Bernadine Healy as NIH director, and mourned the loss of the opportunity to serve the nation. He summed up his experience this way: "If you don't like your boss, quit."

I proposed my theory to Jim—that he was influenced by Bohr—but he actively denied the idea, and offered me a much less convincing exemplar of science that he had chosen as a model, George Gamow. Jim's denials of the parallels with Bohr have, I believe, an odd root. One must assume that Bohr, like Jim, was a brilliant man. But Jim does not regard himself as brilliant. Although Jim does recognize his own genius, I am not sure that Jim regards himself as smart. (By the way, imagine Bohr's self-image, surrounded as he always was with wunderkinder.) I have often heard Jim say, "Scientists do not have to be very smart." I take more to heart this saying of Jim's, "If you are the smartest person in the room, then you have failed."

With time, the parallels to Gamow grew on me. I recalled a title on my childhood bookshelves, *One, Two, Three... Infinity*, with its mysterious cover drawing of the mysterious universe (Gamow 1961). Hadn't Gamow, one of the few physicists with an understanding of general relativity, written popular books on the most difficult of scientific subjects? Long before Stephen Hawking's *Brief History of Time* (Hawking 1988), and the spate of popularized science that followed, Gamow tried to make modern physics accessible. Although that effort failed, certainly one of the successes of molecular biology has been its accessibility. And who might have suggested to Jim that he could write a comprehensible memoir?

THE FUTURE

When finally I did meet Jim in the summer of 1978, in the little office in James lab overlooking the harbor, what struck me as peculiar was not that the office was small, not that he mumbled, not the frequent guttural interruptions of speech. No, Jim was intent

on the future, and although he could not see it clearly, or verbalize it, he wanted to get there first. He was not in the least embarrassed by not knowing precisely how to get there. Just follow your sense. The future would not hide.

This attitude was strange to me. Science, I had thought, was largely the work of cutting through old myths, slaying the false ideas that bind us. But Jim had a different view. The kind of science he pursued was new entirely. There were no false ideas of any strength to struggle against, because the very objects of our inquiry had yet to be experienced. The struggle was to bring new ideas into existence where none had existed before.

I saw this most clearly during the development of Neurobiology at the Lab. Here was a subject for which we had few conceptual handles. The safe thing to do would have been to focus on the development of the nervous system, where techniques similar to those used throughout developmental biology were yielding some solid results. Jim chose instead Learning and Memory. Jim reasoned, why wouldn't this field yield to the same assault of youthful enthusiasm that had sent other walls crumbling down? So we began with fly genetics, a once promising approach that had since been largely discarded by others. Jim hired Ron Davis and Tim Tully and research in Neurobiology at Cold Spring Harbor was reborn. Jim would have started other initiatives, especially in behavioral genetics, but one's energy does not go on forever.

To bring Neurobiology a home, Jim went to his rich friends, asking them to believe in him. They did, enabling Jim to build a lab up on the hill. If I recall correctly, when the plans for the lab on the hill were in the early stages, Jim wanted four bell towers, not just the single one we currently have. One for each nucleotide, I might have asked. No, he said, there should be one for each of the three great religions, and one for the fourth. Which one is that, I inquired. He replied, "The one yet to be discovered." "If we don't try," I imagine him saying, "we will have failed."

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