THE DOUBLE HELIX

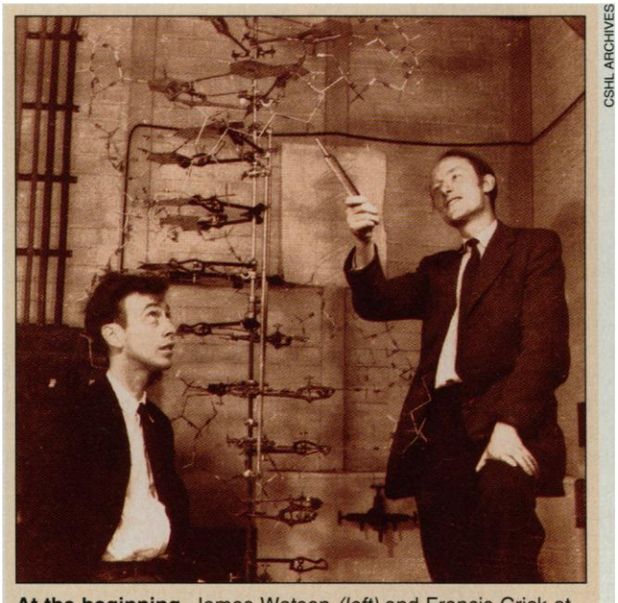
Old School Ties: Watson, Crick, and 40 Years of DNA

For the 130 luminaries gathered at Cold Spring Harbor Laboratory last week to celebrate the 40th anniversary of the discovery of the double helix,* the occasion had a special, unspoken, elegiac quality of an era in biology coming to an end. This sense came partly from seeing and hearing the two protagonists relive that golden moment at this stage of their careers—Francis Crick, who studies the visual system of the brain at the Salk Institute in San Diego, California, turns 77 in June; James Watson, Cold Spring Harbor's longtime director, turns 65 next month. And it came partly from their own remarks: "It's sort of taken 40 years to feel that I'm almost justified finding the double helix," Watson observed at one point.

For Cold Spring Harbor itself, the valedictory tone of Watson's remarks presaged his announcement a few days later, on 5 March, that he would be stepping down at the end of the year as director of Cold Spring Harbor Laboratory after 25 years. Although Watson will remain active and guide overall policy in the newly created position as president, Bruce Stillman, assistant director since 1991, will take over day-to-day scientific operations at the lab, and the move may be the first step toward the end of the Watson era at the lab. He intends to spend a sabbatical in England beginning after the first of the year, and his plans, it is said, include writing his autobiography.

The prospect of a second Watson foray into memoir-writing—given the fireworks set off by the tell-all indiscretions of his first offering, *The Double Helix*—should send shivers through scientific precincts. Yet, to anyone familiar with Watson's flair for appositely blunt overstatement and Crick's talent for sly understatement, last week's meeting revived an anecdote—one of a rich cornucopia offered at the gathering—that suggests just how out of character Watson and Crick's famous 1953 paper may be viewed in retrospect. As Crick delighted in pointing out last week, it was the normally outspoken Watson who insisted on reticence when it came to spelling out the biological ramifications in the paper that first described DNA's structure, which appeared in the 25 April 1953 issue of *Nature*. Watson's exact sentiments on the subject, Crick recalled, were: "The less said, the better..."

That first paper, of course, introduced the double helix as a molecule whose architecture of paired bases accommodated the biochemical requirements of genetic replication and made DNA the much-studied molecule it is today. Terrified that they might be wrong, however, Watson shied from making grand claims. "Jim was very nervous about saying *anything*, and I said, "Well, we've got to say *something*!" said Crick, who—as Watson delighted in pointing out in the opening line of *The Double Helix*—is not regularly given to modest moods. "Otherwise people will think these two unknown chaps are so dumb that they don't even realize the implications of their own work!"



CSHL ARCHIVES

At the beginning. James Watson *(left)* and Francis Crick at the Cavendish Laboratory in 1953.

And so it was that the uniquely self-confident Crick penned one of the great understatements in literature, scientific or otherwise. "It has not escaped our notice," he wrote, "that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." It awaited the often overlooked second Watson and Crick paper, which appeared 5 weeks later (*Nature*, 30 May 1953, p. 964), for the authors to prosecute a more vigorous claim for significance. "If it had been up to me," Crick says now, "the first paper would have been much more like the second. The second paper is much better." No matter. The papers gave molecular biology its charter molecule, and Watson and Crick became as permanently linked by the fame of their discovery as Siamese twins.

"DNA and Biotechnology: A Celebration of 40 Years of the DNA Double Helix" was part reunion, part a view of the future, but mostly a birthday party for a molecule that has made reputations and fortunes for many, including several of the scientific and biotech heavyweights who attended the by-invitation-only event. And though scientists claim to loathe nostalgia, many at the 3-day meeting seemed more than content to hear invited speakers relive historic episodes of molecular biology and recombinant DNA.

Harvard physical chemist Paul Doty recalled the "sense of lightness and playfulness that characterized the fifties," when the first generation of molecular biologists tried to tease out details of the genetic code. Indeed, both Watson and Crick sported the distinctive cravats of the RNA Tie Club—a sinuous, lime-green curl of nucleic acid flanked by boxy yellow outlines of purines and pyrimidines on a black background. Cosmologist George Gamow organized the club in 1954 to investigate the role of RNA in protein synthesis, and its 20 members—one for each amino acid—received a tie and personalized tie clip. (Watson reported that his tie clip read "PRO," for proline, and one biologist pronounced the choice especially fitting; among animo acids, he explained, proline is "kind of an oddball.")

Of all the presentations, the most entertaining was a rollicking, stream-of-consciousness account of the birth of the polymerase chain reaction by Kary B. Mullis of Atomic Tags Inc. in La Jolla. With *Nature* editor John Maddox listening on, Mullis gave a lively and highly subjective account of how, as a biochemistry graduate student at Berkeley in 1968, he wrestled with contentious referees at *Nature* and ultimately convinced the journal to publish his thoughts on the cosmological significance of time reversal. Those thoughts were inspired, he acknowledged, by the sort of "neuropharmacology experiments" that were popular in Berkeley at the time.

Mullis' talk might have stolen the show at another meeting, but this event ultimately belonged to the original bad boys of biology, Watson and Crick. No longer the lanky, leering lad of 1953, Watson now possesses a thinning nimbus of grey hair, a pair of eyeglasses forever migrating north of his ears and south down his nose, and a constant expression of bemusement that belies a considerably less uncertain view of the world; he still has an

*"DNA and Biotechnology: A Celebration of 40 Years of the DNA Double Helix," Cold Spring Harbor Laboratory, 1-3 March 1993.

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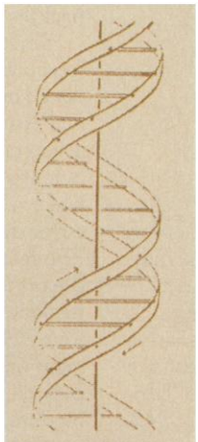
adolescent's restless, evasive eyes, and he still seemed to glance, after all these years, at Crick for approbation as he spoke. Whatever else might be said about Watson's opinionated and often amusing peroration on Tuesday evening, the days of "the less said, the better..." are long gone.

In an hour-long autobiographical ramble, Watson reviewed what he called the "six phases" of his life—student, scientist, professor, administrator, writer, and federal bureaucrat. No Watson talk is without the occasional ad hominem remark, and he slammed outgoing NIH chief Bernadine Healy as "totally incompetent" without further elaboration. But when he wasn't relying on glib outrage for laughs, Watson retreated into those moments of lucid, self-aware, and discomfiting candor that make him an unpredictable and highly entertaining speaker. Of his initial ambition to become an ornithologist and seek work in a wildlife refuge in the West, he said: "That was the idea: birds, no people. Because I didn't know how to talk to people." Of his time at Indiana University, where he studied with Salvador Luria and cut his teeth with the Phage Group, he said: "You've got to sort of reject the people who have supported you, because you've got to start thinking differently from them. I had to say, 'Phages *bore* me!' You know, phages aren't going to tell you anything. You gotta go to the DNA."

Cold Spring Harbor, he recalled, was a bit "rundown" when he first visited it as a graduate student, but he clearly experienced the comforts of an intellectual home for the first time. "The first summer he [Luria] brought me here to Cold Spring Harbor," Watson reminisced, "and that sort of completed my total liberation because there were all these wonderful people here, whose sole ambition was not to make money but: What was the gene? There was only one question: What was the gene? It was *paradise*!"

Those formative years imbued Watson with a set of philosophical rules, which he breezily imparted under the rubric: How do you succeed as a scientist? Among them were: "You've got to try and be with people who are brighter than yourself," "You've got to be prepared sometimes to do some things that people say you're not qualified to do," and "Since you know you're going to get into trouble, you ought to have someone to save you after you're in deep shit. So you better always have someone who believes in you."

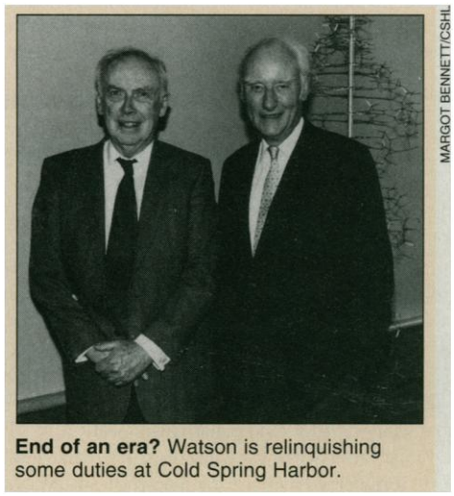
Watson's "rules" go a long way toward explaining how a 24-year-old crewcut American who knew nothing about x-ray crystallography and a loquacious 36-year-old physicist who knew nothing about genetics, working in a physics laboratory on a biological problem they weren't supposed to pursue, could solve the structure of DNA without doing a single experiment themselves.



Odile Crick's best-known work. Francis Crick's wife, Odile, an artist, drew this diagram, which appeared in the first DNA paper.

Watson arrived at the Cavendish Laboratory in Cambridge in 1951. At the time it was headed by Sir Lawrence Bragg, and Crick had already managed to alienate most of his fellow labmates with his know-it-all chatter. "Bragg had just one ambition," Watson noted, "which was to get Francis out of Cambridge." Watson later suggested that within half an hour of meeting Crick for the first time, they discussed the structure of DNA.

Crick, then as now, is a tall, narrow-shouldered, and affably guarded man whose wry and elegant locution reflects both the quickness of his wit and the precision of his thinking. In recalling how science was done in those days at the Cavendish, Crick might as well have been an archeologist describing puzzling quotidian habits in ancient Egypt. "Well, we didn't rush in to work in the morning, let me put it that way," he said of the "very much more relaxed" pace. Watson and he had virtually no visitors to entertain, few seminars to attend, hardly any mail to sift though, he explained; no late nights in the lab (although Crick recalled clambering "quite a number of times" over the Cavendish's locked metal gates after hours to check on crystallography experiments); no grant applications to fill out, no reports to write; hardly any literature to read.



MARGOT BENNETT/CSHL

End of an era? Watson is relinquishing some duties at Cold Spring Harbor.

What they did do was talk—so much so, Crick recalled, that when an extra room at the Cavendish became available, Max Perutz and John Kendrew told Crick, "We're going to put Jim and you in the same office, and you can talk to each other and not disturb the rest of us." With 40 years of hindsight, it may be that Watson and Crick's most powerful scientific technique was just that: a series of astute, rudely rigorous conversations. The combination of constant intellectual jabbering and model-building allowed them to close in on a plausible DNA structure and keep a step ahead of other formidable workers interested in the problem, including Linus Pauling at Caltech and the King's College group in London, Maurice Wilkins and Rosalind Franklin. Of the latter, Watson said: "She would be famous for having found DNA if she'd just talked to Francis for an hour."

By such tinkering and talking, Watson and Crick produced the double helix. Key to the Watson-Crick structure, more even than the two entwined helical backbones of sugar and phosphate atoms, was the paired linkage of purine and pyrimidine bases, held fast by hydrogen bonds; the fact that adenine (A) paired only with thymine (T), and cytosine (C) only with guanine (G), allowed each strand to become a template for the other during replication, an essential requirement of a gene. The illustration of the helix that appeared in the first *Nature* article was drawn by Crick's wife, Odile, an artist. "I tell her it's her best-known work," he said. "She normally draws nudes."

How was the double helix received? "Well now, most people of course feel that once you've seen the structure, the whole world stood up and cheered and everybody started working on it, and the whole scientific community was convinced," Crick recalled. "Not a bit of it, not a bit of it!" Geneticists on the whole seemed kindly disposed, but he recalled that prominent biochemists were not impressed; Erwin Chargaff at Columbia, for example, thought it was "a lot of nonsense, which I'm afraid," Crick added gently, "was a misjudgment." Enlisting the biochemists ultimately turned out to be crucial, however, because they were the ones capable of elucidating the genetic code. "It was perfectly clear to Jim and I that we had to get involved with biochemists," Crick says now, "but it wasn't clear to the biochemists that they had to get involved with *us*."

It fell to Crick to provide the best epilogue to the first 40 years of the double helix. "One has to reflect on, really, what a remarkable thing it is in the history at least of life on Earth," he reminded his audience, "because nucleic acids, certainly RNA and DNA, almost surely existed on the earth for *billions* of years. It is the basis of *all* the lifeforms we see, but really, it's only been in the last half-century—which is a blink, really, in time—that any form of life on Earth has become *aware* of the structure of DNA."

–Stephen S. Hall

Stephen S. Hall is a New-York based science writer.