PNAS RETROSPECTIVE

James D. Watson (1928–2025): Influencer of science and society

Jan Witkowski[a,1] and Bruce Stillman[a]

James Dewey Watson who died on November 7, 2025, at the age of 97, was a towering figure in 20th century life science. With Francis Crick, he determined the structure of DNA, laying the foundation of modern biology; he made Cold Spring Harbor Laboratory one of the world's great biomedical research institutes and a center for professional education in molecular biology and neuroscience; he established the Human Genome Project and ensured that research on the associated ethical, legal, and social issues was part of the project; he created a classic textbook that revolutionized the style of the genre; and he wrote one of the most interesting and controversial books on science for scientists and nonscientists alike.

Watson was born in Chicago on April 6, 1928. His interest in science was sparked by bird watching with his father and visits to the Field Museum of Natural History. He entered the University of Chicago in 1943, age 15, and on graduating in 1947, Watson went to the Indiana University and, having decided that the gene was more important than bird migration, he joined Salvador Luria's laboratory to do his PhD on phage genetics. Luria, with Max Delbrück and Alfred Hershey, was a founding member of the Phage Group, researchers who were using bacteriophages as the subjects for genetic research. Watson's thesis research on the effects of X-rays on bacteriophage multiplication was, he thought, boring, but his association with Luria gave him an entrée to the emerging elite of molecular geneticists.

Inspired by Erwin Schrodinger's *What is Life?* (1), Watson decided that determining the chemical nature of the gene was the key to understanding life. He went to Herman Kalckar's nucleic acid biochemistry laboratory in Copenhagen but found biochemistry uninspiring. Things changed when Watson heard a talk on nucleic acids by Maurice Wilkins from King's College, London. Wilkins showed an X-ray diffraction picture of DNA that set Watson's heart racing. He recognized that X-ray crystallography was the tool for solving the structure of DNA and hence of the gene.

By the end of 1951, Watson was in the Medical Research Council's Unit for Research on the Molecular Structure of Biological Systems at the Cavendish Laboratory in Cambridge, England. There Max Perutz and John Kendrew were working on the structures of hemoglobin and myoglobin. Kendrew's PhD student was Francis Crick and Watson "immediately discovered the fun of talking" to him. Linus Pauling had discovered the alpha-helix of protein molecules by building molecular models and Watson and Crick resolved to tackle the structure of DNA using Pauling's strategy.

Maurice Wilkins and Rosalind Franklin at King's College, London, were also working on DNA but personal incompatibilities between Franklin and Wilkins doomed any collaboration between them. Watson and Crick's first model, a triple helix with the bases on the outside, was shot down by Franklin as being chemically impossible. Later, inspired by the famous Photograph 51 taken by Franklin's PhD student, Ray Gosling, and using additional data from a seminar given by Franklin and from a report on the work of Randall's group, Watson and Crick built the iconic two-chain molecule of DNA. The key insight came when Watson, using cardboard cutouts of the nucleotides, recognized that a regular, double-stranded

Jim Watson at his desk at Cold Spring Harbor. Photo by Mirium Chua (April 2003), copyright Cold Spring Harbor Laboratory.

Author affiliations: [a]Cold Spring Habor Laboratory, Cold Spring Harbor, NY 11724

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[1]To whom correspondence may be addressed. Email: witkowsk@cshl.edu.

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molecule could be made if deoxyadenosine paired with thymidine, and deoxyguanosine paired with deoxycytidine, with the base pairs on the inside of the double helix. Three papers from Watson and Crick (2); Wilkins et al. (3); and Franklin and Gosling (4) appeared in the April 25, 1953, issue of *Nature,* three weeks after Watson's 25th birthday. Crick, Watson, and Wilkins received the 1962 Nobel Prize in Medicine of Physiology for this discovery, with Franklin ineligible due to her untimely death in 1958 from ovarian cancer. Watson received many other awards and honors, too numerous to list here.

DNA was not the only structure that Watson solved at Cambridge. Using X-ray crystallography, Watson determined that the coat protein subunits of Tobacco Mosaic virus (TMV) were arranged helically around the viral RNA, although he could not detect the RNA (5). Two years later, Rosalind Franklin, now at Birkbeck College with J. D. Bernal, published the definitive study on the structure of TMV (6).

Watson left Cambridge in 1953 to take up a fellowship with Delbrück at the California Institute of Technology. He joined forces with Alex Rich in Pauling's laboratory to work on the structure of RNA, but RNA gave fuzzy X-ray diffraction patterns and provided no clues as to what an RNA molecule might look like. Watson was not happy in Pasadena and, with the help of Paul Doty, was appointed an assistant professor in the Department of Biology at Harvard. However, he first spent a year in Cambridge, United Kingdom, before moving to Cambridge, Massachusetts.

Watson and Crick teamed up again to study the structure of small viruses and proposed that as a general principle, the outer protein coat of these viruses was built up of identical subunits. Franklin was also studying small viruses, and she and Watson exchanged letters, and she asked Watson and Crick to review drafts of her manuscripts.

At Harvard, Watson, his colleagues, and students made many important findings on ribosomes and protein synthesis, including demonstrating, concurrently with the team of Sydney Brenner, Francois Jacob, and Matt Meselson, the existence of messenger RNA. Watson's contributions are not reflected in many of the publications from his Harvard laboratory. He did not add his name to papers unless he had made substantial contributions to them, thus ensuring that the credit went to those who had done the work. These papers included the discovery of the bacterial transcription protein, sigma factor, by Watson's then graduate student Richard Burgess, along with Harvard Junior Fellow Richard Losick. At Harvard, Watson also promoted the careers of women, notably providing support for Nancy Hopkins, Joan Steitz, and Susan Gerbi. He also contributed to the split in the Department of Zoology due to his contempt for those working in the Department who were antireductionists.

In his last scientific paper (7), published in 1972, Watson returned to DNA. In considering the replication of linear DNA of T7 phage, he pointed out that the very ends of a linear DNA molecule cannot be replicated, the "end replication problem" which is solved in eukaryotes by telomeres. (Watson's work was predated by Alexey Olovnikov who had published the same observation in 1971 in a Russian journal.)

Administrator

In 1968, Watson became director of Cold Spring Harbor Laboratory (CSHL). He had returned there almost every year since his first visit in 1948 and had been appointed a Trustee in 1964. 1968 was a significant year in another way—he married Elizabeth Lewis, a Radcliff graduate. Liz's contributions to the Watson years at the Laboratory cannot be overestimated. Her training as an architectural historian and arborist proved invaluable and the beauty of the Laboratory's buildings and grounds owes much to her judgment. Together, they had two boys, Duncan and Rufus.

E. O. Wilson had written in his autobiography that he would not have put Watson in charge of a lemonade stand, and yet Watson rejuvenated research at CSHL and turned the Laboratory into one of the world's great research institutes.

Watson did not run a laboratory when he came to CSHL, choosing instead to devote his energies to reviving the Laboratory. He focused research at CSHL on cancer, specifically the DNA tumor viruses adenovirus and Simian Virus 40. This decision proved to be insightful, since studies on adenovirus led to the discovery of RNA splicing, of cooperating oncogenes, of oncogenes counteracting tumor suppressor genes, while studies on SV40 resulted in understanding integration of oncogenes in cells and important insights into the processes of DNA replication and gene transcription. Parallel studies at CSHL promoted by Watson included research on human cancer, resulting in the discovery of the first human oncogene, hRAS, and the discovery of key regulators of cell proliferation, including Cyclin D-CDK4 and its inhibitor p16. In doing so, CSHL contributed significantly to the development of molecular biology in mammalian cells.

Education

CSHL meetings had begun in 1933 and courses in 1945. Watson greatly expanded both programs, using them to promote fields of research he thought important. The course program was an especially effective tool, training a new cadre of young scientists skilled in the necessary techniques. In 1968, there was only one meeting and four courses; in 1978, there were 8 meetings and 12 courses. The Banbury Center became the venue for small discussion meetings on topics across the life sciences, and if the topics were controversial, so much the better. At the other end of the educational scale, Watson enthusiastically supported and encouraged the creation of the CSHL DNA Learning Center which brought hands-on, laboratory-based genetics education to high school children. The DNA Learning Center became the model for similar programs throughout the world. In 1998, Watson achieved a cherished ambition when the Laboratory's graduate school was opened.

For many years, the Laboratory had published the proceedings of the annual Symposium and Watson, as he did with the meetings and courses programs, used the Cold Spring Harbor Laboratory Press to promote research topics he knew were important. The most notable example was the instruction manual, *Molecular Cloning*, based on a course at the Laboratory (8). Providing detailed descriptions of the experimental techniques used in recombinant DNA, it

introduced generations of scientists to these methods and rapidly became a best-seller for the Press.

The Human Genome Project

Watson the administrator moved onto the national and international stage in 1989 when he became director of the Human Genome Project (HGP). Watson had played a vocal role in early discussions, insisting that the project must be run by a scientist and not by a bureaucrat. While many doubted that Watson would be able to function at the NIH and before Congress, his status, and his unrelenting commitment to succeed drove the early days of the HGP. He was able to forge (and force) consensus, and although there were controversies, the foundations of the HGP were laid during his tenure.

Watson was not afraid to make social policy decisions. At the press conference announcing his appointment as director of the Center for Human Genome Research, and without consulting his staff or the NIH director, Watson said that he intended to divert 3% of the HGP research budget to ethical, legal, and social issues (ELSI). Not only was it unprecedented for a federal employee to modify a Congressionally mandated budget, it was an unprecedented amount of money for bioethics. Congress eventually allocated 5% of the Human Genome Project to the ELSI program.

It was Watson's dedication to ensuring that the fruits of the HGP be freely available for improving health that forced his resignation in 1992. Watson learned that Frederick Bourke, an entrepreneur, had invited John Sulston and Bob Waterston, key players in the HGP, to join his company. Watson thwarted Bourke's plans who then complained to Bernadine Healey, the director of NIH, that a federal official was obstructing his business. Healey instructed the NIH counsel to investigate and also to determine whether Watson improperly held shares in pharmaceutical and biotechnology companies. Despite assurances from the NIH counsel that Watson had committed no improprieties, in 1992, he chose to resign. By then, Watson had accomplished his goals–the HGP was established and its budget secure. He continued to play an influential if indirect role in the HGP; the annual CSHL *Genome Mapping and Sequencing* meetings provided opportunities for Watson to bend the ears of leading lights of the HGP.

Author

When Watson began lecturing at Harvard, no undergraduate textbook covered the field of molecular genetics, and so he wrote his own, bringing about a revolution in the style of textbooks. *Molecular Biology of the Gene* (*MBOG*) (9), first published in 1965 and now in its 7th edition, was a remarkable creation. The pages looked attractive, with declarative concept subheadings that informed the reader. Watson was the sole author on the first three editions, but beginning with the fourth edition, the burden of revising the book was increasingly shouldered by others. *MBOG* was followed in 1983 by *Molecular Biology of the Cell* (10) where Bruce Alberts was the lead author. A third textbook, *Recombinant DNA: A Short Course,* appeared in 1985 (11), introducing students to the brave new world of genetic engineering.

If the double helix brought Watson to the attention of the scientific world, his 1968 account of the discovery, *The Double Helix* (12), brought him to the attention of the general public. Watson wrote *The Double Helix* in the voice and with the perspective of the 22-year-old who came to the Cavendish seeking fame and fortune. It was written in the style of a novel and made no pretense to be an academic, historical account. The book introduced the lay world to process and people of science that led to a seminal discovery in biology. Its impact on the general public is evident from the fact that the book has never been out of print, with a new edition, *The Annotated and Illustrated Double Helix*, appearing in 2012 (13).

A Life Not without Controversy

Best seller though it became, publication of *The Double Helix* was not well received by everyone. As Peter Medawar wrote in his review of the book (14), "Like all good memoirs it has not been emasculated by considerations of good taste." Good memoir or not, Crick and Wilkins thought it in very bad taste, presenting, as Wilkins put it, a "distorted and unfavorable image of scientists." They threatened lawsuits if Harvard University Press published the book. Harvard capitulated to their demands and reneged on the contract. *The Double Helix* continues to be controversial to the present day for Jim's portrayal of Rosalind Franklin.

Watson's public pronouncements were frequently controversial, both in topic and style. In the mid-1970s, Watson became entangled in the recombinant DNA controversy, a debate about the safety and regulation of genetic engineering. He signed the "Berg letter," published in *Science* (15), arguing for a moratorium on this research, only to be followed by arguing vehemently against such a moratorium at the 1975 Asilomar meeting.

In the late 1990s, Watson gave seminars, notably at the University of California Berkeley, where he expanded on research on the hormone POMC and related peptides and made inappropriate and incorrect observations about women. In October 2007, he made racist remarks about the intelligence of people of African descent, and, damagingly for his fellow employees at CSHL, stated that while he hoped that everyone was equal, "people who have to deal with black employees find this not true." The CSHL Board of Trustees dissociated the institute from Watson's comments, and he was forced to step down from his administrative position as Chancellor. The matter resurfaced in January 2019 when Watson was asked if his views on race and intelligence had changed. His answer was unequivocal: "No, not at all." The Laboratory's response was immediate, relieving him of all his emeritus titles. Watson and his family, however, continued to live on the CSHL campus.

Conclusion

Working with Jim was remarkable. He was a fount of ideas, of varying degrees of practicality, and there was hardly a discussion with him that ended without there being one or two good ideas to be pursued. His skill at recognizing and recruiting talented young scientists was legendary, providing them with an environment for innovative, independent investigation. Jim was passionate about the Laboratory, and he

proved adept at fundraising. Jim and Liz were devoted to ensuring the beauty of the grounds and buildings; they contributed many of the works of art that grace the Laboratory. Although it used to be said that you had not arrived at Cold Spring Harbor until Jim had fired you at least twice, he and Liz were extraordinarily kind, especially to young people.

Jim's remarkable contributions to science and society will long endure—for the scientists using the human genome sequence, for students using *Molecular Biology of the Gene* and for readers of *The Double Helix,* and for reviving Cold Spring Harbor Laboratory. He was a most amazing man.

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