

## Rosalind Franklin and the Double Helix

Although she made essential contributions toward elucidating the structure of DNA, Rosalind Franklin is known to many only as seen through the distorting lens of James Watson's book, *The Double Helix*.

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In 1962, James Watson, then at Harvard University, and Cambridge University's Francis Crick stood next to Maurice Wilkins from King's College, London, to receive the Nobel Prize in Physiology or Medicine for their "discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material." Watson and Crick could not have proposed their celebrated structure for DNA as early in 1953 as they did without access to experimental results obtained by King's College scientist Rosalind Franklin. Franklin had died of cancer in 1958 at age 37, and so was ineligible to share the honor. Her conspicuous absence from the awards ceremony--the dramatic culmination of the struggle to determine the structure of DNA--probably contributed to the neglect, for several decades, of Franklin's role in the DNA story. She most likely never knew how significantly her data influenced Watson and Crick's proposal.

Franklin was born 25 July 1920 to Muriel Waley Franklin and merchant banker Ellis Franklin, both members of educated and socially conscious Jewish families. They were a close immediate family, prone to lively discussion and vigorous debates at which the politically liberal, logical, and determined Rosalind excelled: She would even argue with her assertive, conservative father. Early in life, Rosalind manifested the creativity and drive characteristic of the Franklin women, and some of the Waley women, who were expected to focus their education, talents, and skills on political, educational, and charitable forms of community service. It was thus surprising when young Rosalind expressed an early fascination with physics and chemistry classes at the academically rigorous St. Paul's Girls' School in London, and unusual that she earned a bachelor's degree in natural sciences with a specialty in physical chemistry. The degree was earned at Newnham College, Cambridge in 1941.

From 1942 to 1946, Franklin did war-related graduate work with the British Coal Utilization Research Association. That work earned her a PhD from Cambridge in 1945, and an offer to join the Laboratoire Central des Services Chimiques de l'Etat in Paris. She worked there, from 1947 to 1950, with Jacques Mering and became proficient at applying x-ray diffraction techniques to imperfectly crystalline matter such as coal. In the period 1946-49, she published five landmark coal-related papers, still cited today, on graphitizing and nongraphitizing carbons. By 1957, she had published an additional dozen articles on carbons other than coals. Her papers changed the way physical chemists view the microstructure of coals and related substances.

Franklin made many friends in the Paris laboratory and often hiked with them on weekends. She preferred to live on her own modest salary and frustrated her parents by continually refusing to accept money from them. She excelled at speaking French and at French cooking and soon became more comfortable with intellectual and egalitarian "French ways" than with conventional English middle-class customs. Consequently, she did not fit in well at King's College, where she worked on DNA from 1951 to 1953. Franklin chose to leave King's and, in the spring of 1953, moved to Birkbeck College. Many of the students there were evening students who worked during the day, and Franklin was impressed with their dedication. After the move to Birkbeck, she began her celebrated work with J. Desmond Bernal on RNA viruses like tobacco mosaic virus (TMV). She was a cautious scientist who began to trust her intuition more as she matured. She published 14 papers about viruses between 1955 and 1958, and completed the research for three others that colleague Aaron Klug submitted for publication after her death.

In his obituary for Franklin, Bernal described her as a "recognized authority in industrial physico-chemistry." In conclusion, he wrote, "As a scientist, Miss Franklin was distinguished by extreme clarity and perfection in everything she undertook. Her photographs are among the most beautiful of any substances ever taken." (1)

## Discovery of two forms for DNA

Franklin's most famous and controversial work yielded critical data that Watson and Crick used to determine DNA's structure. DNA is a double-helical molecule roughly in the form of a spiral staircase. The double-helical molecule, consisting of two unbranched polynucleotide chains, is best visualized by imagining it straightened into a ladder. The side rails of the ladder are each made up of alternating sugar and phosphate groups, linked by so-called 3' or 5' phosphodiester bonds. The sequence of the atoms in each rail runs in opposite directions, so the two sides of the molecular backbone are often described as antiparallel to each other. The rungs of the ladder consist of specific hydrogen-bonded horizontal pairs of nitrogenous bases that are attached to the deoxyribose sugars in the backbone's side rails. Birkbeck's Sven Furberg, who studied both the nucleoside and nucleotide of one of the bases, cytosine, in 1949, discovered that the base would be perpendicular to the sugar: The result can be extrapolated to hydrated DNA. (2)

The pairs of nitrogenous bases that make up the rungs are in the keto, as opposed to enol, tautomeric configurations. (The two are distinguished by the locations of hydrogen atoms available for hydrogen bonding.) The smaller single-ringed pyrimidines, cytosine (C) and thymine (T), are always paired with larger double-ringed purines, guanine (G) and adenine (A). Indeed, the consistent pairing of G with C and of A with T, as first proposed by Watson, explains the identical size of the ladder rungs and also Erwin Chargaff's 1952 observation that G and C (and likewise A and T) are always present in DNA in approximately equal amounts. The consistent pairings, along with the irregular linear vertical sequence of the bases, underlie DNA's genetic capacity.

In an experiment carried out shortly after she arrived at King's, Franklin identified two distinct configurations, called by her the A and B forms, in which DNA could exist. Her work, first presented in an internal King's seminar in November 1951 and published in *Nature* in 1953, was essential for determining the structure of DNA. Researchers working prior to Franklin's discovery invariably had to deal with confusing x-ray diffraction patterns that resulted from a mixture of the A and B forms.

The drier crystalline A form contains about 20% water by weight and is optimally produced at about 75% relative humidity. Cation (for example, Na<sup>+</sup>) bridges between ionized phosphates are probably responsible for intermolecular linking in the crystalline structure. The less ordered, fully hydrated, paracrystalline B form--typically the configuration that occurs in vivo--is obtained from the crystalline A form when DNA fibers absorb water in excess of 40% of their weight. Optimal production of the B form occurs at approximately 90% relative humidity. Extra hydration makes it easier for the molecule to assume the lowest-energy, helical configuration. It also keeps the two helical backbone chains farther apart than in the A form and elongates the molecule by about 30% until the B form appears with its bases oriented perpendicular to the fiber axis.

Franklin slowly and precisely hydrated then dehydrated her DNA sample to obtain her best pictures of the A form. To get her samples, though, she had to extract DNA fibers from a gel-like undenatured DNA sample that Wilkins had acquired from Rudolf Signer of the University of Berne in Switzerland. Franklin pulled exceptionally thin single fibers and controlled the humidity in her specimen chamber by bubbling hydrogen gas through salt solutions and then flooding the chamber with the humid gas that resulted. Franklin's PhD student, Raymond Gosling, told me that the chamber leaked so much hydrogen gas that he was afraid they would blow themselves up accidentally and take half of King's College with them.

Franklin's careful treatment during the transformation from crystalline A-form to hydrated B-form DNA resulted in such a drastic size change that, according to Gosling, the elongating specimen practically "leaped off the stage." After designing a tilting microfocus camera and developing a technique for improving the orientation of her DNA fibers in the camera's collimated beam, Franklin took x-ray diffraction photographs of the B form.

Franklin's B-form data, in conjunction with cylindrical Patterson map calculations that she had applied to her A-form data, allowed her to determine DNA's density, unit-cell size, and water content. With those data, Franklin proposed a double-helix structure with precise measurements for the diameter, the separation between each of the coaxial fibers along the fiber axis direction, and the pitch of the helix (3).

The resolution of the B-form photograph #51 shown allowed Franklin to determine that each turn of the helix in the B form is 34 Å long and contains 10 base pairs separated by 3.4 Å each (3), in accordance with

less precise data obtained by William Astbury and Florence Bell in 1938. (4) Wilkins, photographing living sperm cells in 1952, obtained an X-shaped B-form diffraction pattern similar to Franklin's. Her photograph, though, showed much more detail.

### **Additional contributions**

The cylindrical Patterson map calculations that Franklin applied to the A-form of DNA were the first such calculations applied to any molecule. They confirmed her suggestions that the hydrophilic sugar phosphates form the external backbone of the DNA molecule and that the hydrophobic base pairs are protected inside that backbone from the cell's aqueous environment. The calculations also allowed her to deduce that the A-form helix has two antiparallel chains. With Gosling, Franklin provided details of the physical distortion accompanying the dehydration transformation from B-form to A-form DNA (5). She also showed that the bases of the A form are tilted and curved slightly, and that 11 pairs of bases are compacted within a repeat distance of 28.1 Å.

In her section of the 1952 King's Medical Research Council (MRC) report, Franklin gave quantitative measurements for the interphosphate distances and discussed the external placement of the phosphates. Her presentation was instrumental in getting Watson and Crick to abandon their earlier attempts at placing the bases on the outside of their model. Initially, they (and Linus Pauling, too) mistakenly thought that the bases would have to be externally accessible in order to pass genetic information.

In May 1952, Franklin presented her clearest evidence of the helical backbone, with her diffraction photograph #51. Although she did not yet realize how the nitrogenous bases are paired or that the helical backbone rails of B-form DNA are antiparallel, her notebook entries starting in January 1951 clearly show that she was making significant progress toward solving those two final aspects of DNA structure. After reading an article by June Broomhead (6), and studying other related papers, she had used the keto configuration for at least three of the four bases. She was aware both of Jerry Donohue's work concerning tautomeric forms of bases and of Chargaff's work.

Astbury and Bell's earlier, less clear diffraction photographs and later data of Wilkins suggested some of the data that Franklin derived from her photograph #51. But Franklin's results were much more precise than the Astbury and Bell data, which showed neither an X pattern nor layer lines. Astbury and Bell themselves described their results as "still rather obscure." After Oxford crystallographer Dorothy Hodgkin helped her to eliminate two of three possibilities she had calculated, Franklin described the correct crystallographic space group for DNA in the 1952 MRC report.

Only after Crick obtained Franklin's data--his thesis adviser, Max Perutz, agreed to give him a copy of the 1952 report and Watson had seen photograph #51--was he sufficiently convinced to start constructing the backbone of the successful DNA model. He recognized the similarity of the space group Franklin had calculated to that of his thesis molecule, hemoglobin, and immediately deduced that there would be an antiparallel orientation between the two DNA coaxial fibers. Within one week, he started modeling the correct backbone in a manner compatible with Franklin's data. On several occasions, Crick has acknowledged that the data and conclusions in the 1952 report were essential.

### **Franklin's 17 March 1953 draft**

On 18 March 1953, Wilkins penned a letter acknowledging receipt of the Watson and Crick manuscript that described the structure of DNA. A day earlier, Franklin, who was preparing to leave for Birkbeck, polished an already written draft manuscript outlining her conclusions about the double-helix backbone chain of B-form DNA (7). Franklin only slightly modified her draft to prepare her April 1953 *Nature* paper, which appeared as the third in a series that led off with the famous Watson and Crick proposal. Partly as a consequence of its placement, Franklin's paper seemed merely to support Watson and Crick's work. But Franklin's data played far more than just a supporting role--as early as 1968, Watson's *The Double Helix* tells us so.

Ironically, despite its negative portrayal of Franklin, *The Double Helix* was what first brought

widespread attention to Franklin's key contributions to the Watson and Crick proposal. The book describes how Watson and Crick built their first, and incorrect, model right after Watson inaccurately reported Franklin's November 1951 seminar data to Crick. It also details how, after 13 months of inactivity, they built their correct model once Wilkins showed Franklin's photograph #51 to Watson, and Perutz showed Crick the 1952 MRC report.

The importance of Franklin's work to the discovery of DNA structure has not been well documented until recently for a variety of reasons too long to discuss here. Relevant issues include women's being underrepresented in historical accounts, although several authors have striven to correct that imbalance (8); Watson and Crick's routinely citing the more senior Wilkins before Franklin; and Wilkins's repeating much of Franklin's work. In addition, Wilkins, not Franklin, was nominated for membership in the Royal Society even though, at the time of his nomination, Franklin was famous for her TMV accomplishments.

### **Conflict within the King's MRC**

Franklin was an outstanding and accomplished scientist--a fascinating individual with a strong personality who made a lasting impression on almost everyone she met. Throughout her career, she routinely ate lunch amicably with both male and female colleagues and most of her acquaintances liked her. Her numerous lifelong friends thought her bright, fascinating, witty, and fun. Most of her lunchtime colleagues at King's would agree with that description, but only as it pertained to her lunchtime persona. When Rosalind headed for the laboratory, she shed almost every vestige of lightheartedness as she focused exclusively on her work.

Furthermore, in what amounted almost to social heresy in England, en route to her laboratory she typically bypassed the morning coffeepot and afternoon tea in favor of a direct assault on her work. Franklin was considered by King's colleagues to be "too French" in her dress, in her intellectual interests, and in her temperament. She was exceedingly direct, intent, and serious, with the tendency to leap into passionate debate. She could be assertive, uniquely stubborn, argumentative, and abrasive to the point that colleagues, especially Wilkins, sometimes found her unpleasant.

On the rare occasions when Franklin departed from her typical behavior, King's colleagues usually did not even notice--they took her seriously at all times. That became especially important when she created a "death of the helix" funeral invitation as a joke after obtaining some data indicating that A-form DNA is nonhelical.

Whereas Franklin was quick, intense, assertive, and directly confrontational, Wilkins was exceedingly shy, indirect, and slowly calculating to the point of appearing plodding. Almost all testimony from King's staff indicates that any blame for their perpetual conflict needs to be shared. John Randall, director of the MRC, also deserves some share of the blame. Without informing Wilkins, he wrote a letter to Franklin assigning DNA structural studies to her. He also did not warn Franklin about Wilkins's continuing interest in DNA.

Randall and Wilkins did make some important accommodations for Franklin. They hired her into a senior position based on her expertise. They gave her an excellent laboratory, the highest quality DNA, and a decent budget. However, numerous MRC women, although very well treated for that era, did not receive precisely equal treatment with men. Taken as a whole, the King's MRC women did not rank quite as highly as the men. Also, Gosling told me that women were not allowed upstairs for after-lunch coffee in the smoking room, "a wonderful long room," he explained, "with window seats." That exclusion undoubtedly cut off a natural route for easy scientific conversation.

Franklin's tenure at the MRC ended on an unfortunate note. As a condition to agreeing to transfer her fellowship to Birkbeck, Randall made Franklin promise not to perform additional experiments on DNA, or even to think about DNA. Moreover, Franklin was forced to leave her diffraction photograph behind at King's and to leave the work of confirming DNA's structure to Wilkins. Personality conflicts were the major source of Franklin's difficulty at King's, and her status as a woman may have made her problems worse. Even today, I and many of my women colleagues find that forcefully aggressive behavior, for example, is usually considered merely irritating when exhibited by a man but is often deemed unacceptable when demonstrated by a woman.

### **Watson's view: *The Double Helix***

In *The Double Helix*, Watson bases his account of Franklin on recollections of their three brief meetings between 1951 and 1953, and on repeated complaints about her from Wilkins. The "Rosy" that Watson describes is a caricature based on the more difficult aspects of Franklin's personality. His portrayal--a far cry from the competent scientist described by her colleagues or the fascinating person described by her friends--is an effective device for promoting the idea that Watson and Crick had to rescue DNA data from--as Watson's book puts it--this "belligerent" woman who could not "keep her emotions under control" and who did not know how to interpret her own data. Watson falsely depicts Franklin as Wilkins's assistant, incapable and unworthy of Nobel Prize-caliber work. His book was published against the vehement protest of key DNA participants, who were upset about its numerous inaccuracies (9).

Unfortunately, Watson's admittedly fascinating, irreverent, and concise book has sold millions of copies and is for many, especially in the US, the primary source of information about DNA history. That such a one-sided account both is presented as historical fact and has had tremendous influence is worrisome. Watson's treatment of Franklin, who was then deceased and not protected by libel laws, is especially troublesome.

Watson's depiction of Franklin went largely unchallenged, at least in print, until Anne Sayre published her 1975 biography *Rosalind Franklin and DNA* (W. W. Norton, 1975). Sayre asked awkward, science-related questions: Why would Franklin give her data to Watson, Crick, and Wilkins, three scientists who seemed to have nothing to offer in return at that time? Where would Watson and Crick be without Franklin's results? Why did they not acknowledge Franklin's contributions clearly and appropriately? Regrettably, Sayre's influence was diminished because she was misled about the conditions for women at the MRC. She mistakenly assumed those conditions to be as problematic as they were at the rest of King's, and therefore incorrectly interpreted Franklin's problems at King's in terms of gender issues. Subsequent accounts, though in many ways excellent, typically are dismissive of gender concerns (10) and personality issues (11). They don't address the awkward questions Sayre raises nor do they sufficiently emphasize that the Watson and Crick model was made possible by Franklin's data. Fortunately, Brenda Maddox's outstanding and comprehensive 2002 biography of Franklin (12) does consider questions of acknowledgment and corrects misconceptions about gender and personality issues. Perhaps it will educate the public more fully than have previous texts.

### **Inadequate acknowledgment**

In their 1953 paper, Watson and Crick state that they had been "stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London." That oblique acknowledgment misrepresented Franklin's role and, whatever its intention, left most people with the impression that her work mainly served to confirm that of Watson and Crick. It has to be one of the greatest understatements in the history of scientific writing.

Given her temper, it is likely that Franklin would have been very angry if she had known the extent to which Watson and Crick used her data. In a 1951 incident, Franklin was furious that a conference acquaintance planned on publishing an idea of hers without giving proper acknowledgment. She shocked him by the tone of her letter in which she demanded coauthorship.

In 1954, Crick and Watson published a detailed methods paper in the *Proceedings of the Royal Society*. In that paper, their acknowledgment of Franklin is often ambiguous. Three of the four times they mention the importance of her data, they link it with mention of Wilkins's data first in a way that suggests the two scientists' contributions were of equal importance. Twice they follow what appears to be a clear acknowledgment of Franklin's contributions with a recanting qualifying statement, for example, "we should at the same time mention that the details of [the King's College's] X-ray photographs were not shown to us and that the formulation of the structure was largely the result of extensive model building in which the main effort was to find any structure which was stereochemically feasible." They might not have known all of the details, but they had access to a significant number of them.

Another lost opportunity for acknowledging Franklin occurred during the 1962 Nobel Prize ceremony.

Neither Watson nor Crick thanked Franklin for making their discovery possible. Indeed, neither mentioned her name, although, according to Wilkins, Crick did ask him to mention Franklin. That request was a dubious shifting of responsibility given Wilkins's antipathy toward Franklin, and Wilkins in fact made only minor mention of her. Crick spoke on the genetic code, which had nothing to do with Franklin's work. Watson spoke on RNA, including RNA viruses. Franklin was an expert on those viruses, yet, in his 59 citations, Watson managed to omit any reference to her work. To this day, Watson emphasizes the opinion that Franklin, although a gifted experimentalist, could not properly interpret all of her own DNA data.

Franklin is prominent in virtually every telling of DNA history, but she is painted differently in various accounts. Watson and Crick made one of the most important and impressive scientific discoveries of the 20th century, but their golden helix is tarnished by the way they have treated Franklin and Wilkins. A meaningful gesture, given that it was Franklin's data that Watson and Crick most directly used, would be for scientists to refer to the "Watson, Crick, and Franklin structure for DNA."

It is important to stop demeaning Franklin's reputation, but equally important to avoid obscuring her more difficult personality traits. She should not be put on a pedestal as a symbol of the unfair treatment accorded to many women in science. Her complicated relationship with Wilkins has been treated in overly simplistic ways. Distorted accounts, which inaccurately portray the three Nobel Prize winners as well as Franklin, are unfortunate and unnecessary: There was enough glory in the work of the four to be shared by them all.

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