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Recognition, Integrity, and the "Secret of Life": Rosalind Franklin and the Discovery of the Double Helix

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SUMMARY: The discovery of the enigmatic structure of DNA was one of the greatest scientific discoveries of the 20th century. In April 1953, James Watson (b. 1928) and Francis Crick (1916-2004), discovered the molecular structure of DNA and published their findings in Nature. A major breakthrough in understanding the structure of DNA, however, came from Rosalind Franklin (1920-1958) who provided a photograph of DNA's double helical structure. Watson himself said that when he saw the photo, "my mouth fell open, and my pulse began to race." This paper examines Rosalind Franklin's contributions to the discovery of DNA's structure, and considers what the modern scientific and medical community can learn from her life and research. It will use biographies of Rosalind Franklin, written by Anne Sayre and Brenda Maddox, as well as her original research data available from the National Library of Medicine.

KEYWORDS: Rosalind Franklin, DNA, Double Helix, James Watson, Francis Crick

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Introduction

Rosalind Elsie Franklin was born on July 25th, 1920, in London, England, to a prominent and wealthy Anglo-Jewish family. The Franklin family, originally among the Ashkenazi Jews of Northern Europe, had been in England for over 200 years. Their immigrating ancestor had anglicized the Jewish name Fraenkel in an attempt to appear less foreign in his new country.[1] Indeed, by the early 20th century, the Anglo-Jewish community

[1] Brenda Maddox, *Rosalind Franklin: The Dark Lady of DNA* (New York: HarperCollins, 2002), p. 3.

of 30,000 that the Franklins were a part of had achieved relative acceptance by the English. They were "a happy breed: secure, able, influential, socially conscious, and cosmopolitan".[2] Strong loyalty to their Judaic faith and family was evidenced by a robust culture of social events and intermarriage. The Franklins, being bankers and publishers, as well as renowned philanthropists, fit right into this society.

Rosalind was the second of five children: three boys and two girls. Her father, Ellis Franklin (1894-1964), worked at his father's bank, and spent many evening hours as a volunteer instructor at The Working Men's College. Rosalind's mother Muriel (1894-1976) was a very intelligent woman, but since higher education for women was frowned upon, she instead employed her talents by being heavily involved in charity work with her husband. The family lived in a large house in what is now Notting Hill. When not busy with other activities, Ellis loved to travel abroad with his family, enjoying long hiking trips and wilderness explorations.

At an early age Rosalind displayed a quick mind, leading an aunt to exclaim, "Rosalind is alarmingly clever – she spends all her time doing arithmetic for pleasure, and invariably gets her sums right."[3] At the age of eleven, Rosalind entered the academically rigorous St. Paul's school, a good match for her competitive nature. Maddox writes that "trouble with teachers, anxiety over marks, [and] delight in science, sport, and sewing" were the norm.[4] Excelling in the fields of chemistry, physics, and mathematics in particular, Rosalind earned a scholarship to Newnham College, Cambridge when she was seventeen. As she left for Cambridge in 1938, her father and family were busying themselves assisting thousands of Jewish refugees fleeing the persecution in Germany.

At Cambridge, Rosalind continued to excel in the natural sciences. The Franklins took a family holiday to Norway in the summer of 1939 after Rosalind's first year, but it was cut short after the worrying news of the Nazi-Soviet non-aggression pact of Brest-Litowsk. Rosalind's father would have preferred that she helped with the war effort, but allowed her to return to Cambridge at the insistence of Rosalind's mother. It was during her second year that Rosalind first became interested in crystal structures and X-ray crystallography (i.e. using X-rays to determine the structure of a crystal). When shown the suggested helical structure of nucleic acids, Rosalind posed the following question in her workbook –

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[2] *Ibid*., p. 5.
[3] *Ibid*., p. 15.
[4] *Ibid*., p. 28.

"A geometrical basis for inheritance?"[5] Near the end of her second year at Cambridge, an ongoing disagreement with her father Ellis over her devotion to science culminated in a dispute; documented in one of her frequent letters to her parents. In the letter, Rosalind explained that her love of science stemmed from its explanation of life. She expressed her faith in mankind, but rejected her father's definition of faith, which she called "belief in life after death."[6] No doubt this upset her parents deeply, but Maddox has suggested that Rosalind remained true to Jewish tradition in her loyalty to family, knowledge, and hard work.[7]

Rosalind's third and final year of her degree at Cambridge was completed while German bombs fell on London. Despite the usual apprehension and insecurity about her performance, Rosalind did very well. Her devotion to her studies also precluded any interest in romance – Rosalind confessed to a cousin that year that she had never been kissed.[8] In 1941, she was awarded her 'degrees titular' – as women were not yet considered full members of the university – and therefore ineligible for degrees. Rosalind was granted a scholarship to stay at Cambridge for a year of post-graduate work in the Department of Scientific and Industrial Research. Unfortunately, Rosalind's new supervisor, Ronald George Wreyford Norrish (1897-1978), gave her a simple project that was no match for her intellect. This patronization, combined with Rosalind's direct and uncompromising personality, led to several confrontations with Norrish.

Rosalind's Early Research

Her desire to contribute to the war effort led Rosalind to accept a position at the "British Coal Utilization Research Association" (BCURA) in 1942. Coal had been used successfully in gas masks in World War One, as its tiny pores were impermeable to many toxic gases. Rosalind's job was to investigate what made certain types of coal more effective in this application. Rosalind excelled at the delicate experimental work and was rewarded with a PhD in physical chemistry in 1945. With her doctorate in hand, Rosalind accepted a job at a French government laboratory in Paris in 1946. She had loved France since the family trips of her youth and also

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5 *Ibid*., p. 56.
6 *Ibid*., p. 61.
7 *Ibid*.
8 Brenda Maddox, *Rosalind Franklin: The Dark Lady of DNA* (New York: Harper Collins, 2002), p. 69.

travelled there with friends during her study breaks at Cambridge. Rosalind jumped at the chance to continue her coal research there.

The laboratory director in Paris was Jacques Mering (1904-1973), a prominent X-ray crystallographer. In contrast to the conventional X-ray methods used for highly-ordered crystals, Mering used modified X-ray methods to take pictures of irregular coal and graphite crystals. He trained Rosalind in these methods, which were a natural addition to her previous research. They often spent long days deep in intellectual discussion and developed a close relationship. Mering was married, but later admitted to being very attracted to her. Rosalind however, being romantically inexperienced, eventually drew back from his advances.[9] Mering eventually moved on to an affair with another young woman in his laboratory. Lingering emotional tension remained in the lab long afterward. Unfortunately, Rosalind and Jacques Mering no longer had the close personal or academic relationship they had shared earlier. Rosalind's work on coal began to garner an international reputation. She was well-spoken at conferences, becoming very knowledgeable in the area of carbon structures and excellent at X-ray crystallography methods. In June 1950, the journal *Acta Crystallographica* published her key findings to date: that some amorphous coals would not transform into the weaker graphite form no matter how much they were heated.[10] This had important applications for the coal-dependent industry. Rosalind hoped to use this academic prestige to obtain a research position back in London. However, she had mixed feelings about returning to England, as she now felt much more of an European woman than an English woman. At the same time, the ongoing tension at the lab in Paris made it impossible to stay, and her parents continually asked when she was coming home.

In June of 1950 Rosalind accepted a three-year research fellowship at King's College in London, working under John T. Randall (1905-1984). She was scheduled to start the following January, focusing on the X-ray diffraction of proteins in solution. Still in Paris, Rosalind wrote Randall a letter in November 1950 wherein she outlined a detailed list of supplies that she would need, most importantly a specialized X-ray tube and camera. Randall's reply changed everything. Maddox writes that his letter was "packed with half-truths and buried meanings that would explode in Rosalind's face before too long and, not incidentally, alter the course of scientific history".[11]

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[9] *Ibid.*, p. 97.

[10] Rosalind E. Franklin, "The Interpretation of Diffuse X-ray Diagrams of Carbon," *Acta Crystallographica* 3 (1950), pp. 107-121.

[11] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 114.

A few months earlier, Maurice Wilkins (1916-2004) and Raymond Gosling (b. 1926) were also working in Randall's laboratory at King's College, had been able to take a better diffraction picture of deoxyribonucleic acid (DNA). This new development suddenly made determining its structure more interesting and likely. Since Rosalind was a more experienced crystallographer than Wilkins, Randall now planned to have her replace Wilkins and work with his student Gosling on the DNA project, rather than the protein project as initially agreed upon. However, Randall failed to tell Rosalind in his letter that she was replacing Wilkins, and also failed to tell Wilkins that she was coming. He also said that Rosalind and Gosling would be working on DNA alone, but in fact, he allowed Wilkins to continue as well. Randall's remarkable lack of clarity over responsibilities and assignments to Rosalind and Maurice Wilkins contributed to the friction between the two. Even before Rosalind had begun, the project was changed and the stage for conflict set.

The History of DNA Research Prior to 1950

In order to understand how Rosalind's DNA research began, it is necessary to recap what was known about genetic inheritance and DNA structure at the time. In the 1920s, protein had been thought to be the likely vehicle for inheritance. With its twenty amino acids, it seemed to have a lot more variability than DNA's four nucleotides; this variability was thought to be necessary to encode the complexities of life. DNA was proposed to be the simple molecule that held the protein together. John Desmond Bernal (1901-1971) and William Astbury (1898-1961), both English crystallographers, worked on the structure of large biological molecules in the 1930s. William Astbury was able to produce the first X-ray diffraction picture of a DNA fibre which showed that the molecule must have a repeating structure. From this pattern, he correctly determined that the bases of DNA lay flat and spaced exactly 3.4 Angstroms apart. The polymeric structure of DNA, with an alternating sugar-phosphate backbone was understood, but the double helical structure of the molecule was not. In 1938, Astbury attempted to build a model of DNA from his preliminary X-ray picture, but this was unsuccessful.

In 1944, the American medical researcher Oswald Avery (1877-1955) had already made an important discovery; pure DNA from a virulent strain of *Streptococcus pneumonia* bacterium was able to transform a harmless strain into a virulent one. He therefore concluded that DNA is responsible for inherited traits and must be the hereditary material rather than protein.[12] But how could a simple molecule with a four letter code be responsible for all the variability of life? Avery and his fellow researchers agreed that the secret of the specificity and complexity of DNA must lie in the details of its structure, which was not yet fully understood.[13] The new methods of biophysics, whose researchers were using X-rays to investigate biological molecules, were regarded as the way to determine the structures of these molecules, including DNA. The hot topic of determining DNA's structure and the secret of the gene appealed to post-war physicists who were looking for a new challenge. Erwin Schroedinger (1887-1961), a prominent German theoretical physicist, gave a series of lectures in 1943 entitled "What is life?" These lectures further stimulated his research community to use its tools to tackle this fundamental question.

In 1948, Linus Pauling (1901-1994), an American chemist, correctly deduced the alpha helical structure of some proteins using X-ray diffraction data and his attempts to build a model that satisfied the X-ray pictures.[14] Wilkins' and Gosling's X-ray diffraction picture of DNA in early 1950 suggested that it too had a helical structure. In 1949, Erwin Chargaff (1905-2002), an American biochemist, made two key discoveries: First, the relative amounts of the bases in DNA corresponded to each other. The amounts of adenine (A) and thymine (T) were the same, and the amounts of cytosine (C) and guanine (G) were the same; but A plus T did not equal C plus G. This was a key hint at the base-pair structure that Watson and Crick would later propose, but Chargaff could not explain the ratios he had found at the time. Second of all, Chargaff showed that the amount of the bases varied from one piece of DNA to another. This showed that DNA was not merely a polymer of repeating ACTG units as previously thought. It also suggested molecular diversity that was previously thought to be lacking.

In 1951, three separate groups had made it their goal to discover the structure of DNA. Linus Pauling was leading a group at the California Institute of Technology. James Watson (b. 1928) and Francis Crick (1916-2004) were working at Cambridge. J.T. Randall's group, including Maurice Wilkins (1916-2004) – and now Rosalind Franklin – were working at King's College in London. They were all trying to answer the same questions: How many chains came together, and in what type of helical arrangement? Do the bases point inward or outward from the

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12 National Library of Medicine, *The Oswald T. Avery Collection*; retrieved on 30 June 2009 (http://profiles.nlm.nih.gov/CC/Views/Exhibit/narrative/dna.html).

13 Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 122.

14 National Library of Medicine, *The Linus Pauling Papers*; retrieved on 30 June 2009 (http://profiles.nlm.nih.gov/MM/Views/Exhibit/narrative/biomolecules.html).

backbone? Can we determine the angles and positions of all the atoms and bonds in order to build a model? The scientific race toward the structure of DNA was on.

Discovering Two Forms of DNA: King's 1951

On January 8th, 1951, J.T Randall arranged a meeting to introduce Rosalind to the other members of the DNA project at King's College. Raymond Gosling (b. 1926), a PhD student who was working with Wilkins, was present at the meeting. Randall reassigned him to work with Rosalind on the DNA project. Alec Stokes (1919-2003), a mathematician who was responsible for the calculations necessary to interpret the diffraction images, was also there. Conspicuous by his absence was Wilkins, who was on holidays when the meeting took place.

The fact that Randall chose to call a meeting without Wilkins further contributed to the rift that would develop between the two. The year before, when Wilkins had heard that Rosalind was coming to King's to study proteins in solution; he suggested to Randall that since she was an X-ray expert, she would work on the exciting new DNA leads with him instead. Randall agreed, and Wilkins therefore felt that he had been influential in getting Rosalind to join the team working on DNA.[15] However, in his letter to Rosalind in 1950, Randall implied that Rosalind and Gosling would be working on the DNA project alone. As a consequence, Rosalind would later interpret Wilkins offers of help as implying that she was incapable of interpreting her own results.

A number of other factors contributed to the animosity between Rosalind and Maurice Wilkins. Since Wilkins was unfamiliar with Rosalind's prior work on coal and mineral graphite in Paris, (where she had been a senior researcher,) he therefore did not appreciate her X-ray skill, and focused more on her lack of experience in the biological realm. Rosalind, on the other hand, viewed Wilkins' skills as inferior to hers and not worthy of his position as assistant director. Their personalities were also polar opposites. Rosalind spoke quickly, and fixed her gaze intently on whomever she was speaking to. She never shied away from a conflict or argument, but clearly told someone if she did not agree with them. Maurice Wilkins was much quieter and calmer; he avoided confrontation and never looked people in the eye. He certainly was not a strong charismatic man like Jacques Mering or Rosalind's father Ellis; men whom Rosalind respected and admired.

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15 Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 130.

Armed with her honed X-ray diffraction expertise, Rosalind set about ordering, setting up, and fine-tuning the equipment she would need to take pictures of DNA. Rosalind was able to develop a technique to closely control the humidity of the DNA fibres. This allowed her to make a key discovery: there were two forms of DNA. At high humidity, the DNA fibre absorbed water and became longer and thinner – Rosalind and Gosling called this the ‘B’ form. When the humidity was lowered, the DNA became shorter and thicker again – they called this the ‘A’ form. Previous pictures had been a mixture of these two forms which made them blurry. Now that Rosalind and Gosling were able to isolate each form separately, they were able to obtain higher resolution images that would allow for more precise calculations about the DNA’s structure. Rosalind also drew an important conclusion from this experiment. She discovered that water could move reversibly in and out of the DNA fibres as she changed the humidity. This meant that the sugar-phosphate backbone, which is hydrophilic (Gr.: water-loving), must be on the outside of the molecule, and the hydrophobic (Gr.: water-repelling) bases on the inside of the structure.[16] Watson and Crick would later miss the significance of her experiment and build their first DNA model with the backbone in the center.

Up to this point, Wilkins and Rosalind had been working totally separate due to their previous disagreements. When Wilkins saw Rosalind’s excellent results, he tentatively suggested that they collaborate. Rosalind saw this as an attempt to explain her own results to him, and got very angry.[17] In fact, she had become so disillusioned with the lab at Kings and London in general that she considered quitting the DNA work and returning to Paris. Their confrontation finally forced Randall to address the issues he had helped create. He negotiated a truce with Rosalind and Wilkins – she would work on the B-form and Wilkins on the A-form. The two ceased to communicate at all. Wilkins appeared to get the short end of the stick. The sample of DNA he was working with was not of the same quality as Rosalind’s and was not giving him the same results. In addition, he did not have Rosalind’s X-ray skill, or her delicately adjusted apparatus. As a result, Wilkins did not make much progress. Rosalind, on the other hand, continued to take more high-quality pictures and draw important conclusions from them.

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[16] National Library of Medicine, *The Rosalind Franklin Papers*; retrieved on 10 June 2009 (http://profiles.nlm.nih.gov/KR/Views/Exhibit/narrative/dna.html).

[17] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 177.

In the meantime, Linus Pauling had published his data on the alpha helix as a protein structure. Doing so meant that he had scooped the Cambridge team working on protein structure, led by his long-time rival Sir William Lawrence Bragg (1890-1971). Many in the biophysics community felt that while model building and deductive reasoning were useful to deduce possible molecular structures, as Pauling had done, the only way to prove that the models were correct was with hard X-ray diffraction pictures. Rosalind too became convinced of this, which is evidenced by her later hesitancy to build a model of DNA until there was enough evidence to back it up. Pauling had since decided to try and deduce the structure of DNA by model building as well. He wrote to Randall and boldly asked for a copy of Wilkins' results so he could try and interpret it, but Randall diplomatically refused.[18]

Frustrated with Rosalind and his own lack of progress, Wilkins began to frequently meet with his fellow crystallographer and friend at Cambridge, Francis Crick. Crick was working on protein crystallography up to that point – no-one at Cambridge was working on DNA yet. Earlier, in May of 1951, Wilkins had presented some King College's data at a conference in Naples, Italy. Present at the conference was a young James Watson, only 23 years old. Watson had first finished his PhD in genetics in Indiana, and had made it his single-minded goal to understand how DNA was responsible for inheritance. Wilkins' presentation showed that DNA had a regular structure that was ripe for understanding, which excited Watson; Watson since transferred to Cambridge, when he met Crick himself. The two clicked immediately, and Watson convinced Crick to drop his protein project in order to help him build a model of DNA. Watson hoped to emulate Pauling's modeling success with the protein alpha-helix and obtain the glory of the gene for himself.

In November the three of them – Watson, Crick, and Wilkins – met at Crick's house in Cambridge. Watson and Crick pressed Wilkins for information about the DNA research, and he obliged. He was fed up with Rosalind, and as far as he knew no-one at Cambridge was working on DNA. Watson also attended a colloquium at King's later that month, where Rosalind presented her results about the A and B-forms of DNA. Watson, not being a crystallographer, did not understand her results and missed the conclusion that the phosphate backbone was on the outside of the molecule. The next week, Watson and Crick completed a DNA model

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[18] Oregon State University, *Linus Pauling and the Race for DNA*; retrieved on 10 June 2009. (http://osulibrary.oregonstate.edu/specialcollections/coll/pauling/dna/people/randall.html).

based on the information they had learned from these two occasions. It contained three helical chains, with the phosphates on the inside and the bases on the outside – contrary to Rosalind's data.[19] Bragg and Crick's immediate supervisor, John Kendrew (1917-1997), insisted on inviting the King's team to visit from London to see what they had done. Upon seeing the model, Rosalind wasted no time in pointing out their mistakes. Subsequently, Bragg told Watson and Crick in no uncertain terms to stop the model building project altogether and return to their previous research. He and Randall had decided not to tread on each other's turf – King's would pursue the structure of DNA alone. Crick returned to his work on protein structure, and Watson went back to work on plant viruses. Watson fully intended to return to model building though; he wrote in a letter to his mentor, Max Delbruck (1906-1981):

> We have temporarily stopped for the political reason of not working on the problem of a close friend. If, however, the King's people persist in doing nothing, we shall again try our luck.[20]

Proving DNA is Helical: King's 1952

In January 1952, Rosalind and Raymond Gosling (b. 1926) began an intense and laborious procedure designed to prove the structure of DNA. They planned and built a rotating camera that allowed them to take X-ray pictures of a DNA strand from many directions. Then they applied a complex series of mathematical equations (functions named after the American crystallographer Arthur Lindo Patterson (1902–1966) to these pictures. Each picture gave a slice of information about what the DNA molecule looked like from that angle. Then Rosalind and Gosling had to assemble the information like a three dimensional puzzle. Wilkins had stopped working on DNA due to his lack of progress, and openly promoted a model-building approach rather than Rosalind's laborious method. In May, Rosalind took her clearest picture yet of the B-form – a clear X-shaped pattern which unequivocally revealed that the B-form was a helix. Rosalind labelled this picture 'Photograph 51', but left it alone for the time being while working on the Patterson functions.

They then turned their attention to the A-form to see if they could attain the same results. However, Rosalind and Gosling obtained conflicting data on the A-form which suggested it may not be a helix.

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[19] National Centre for Biotechnology Education, *Double Helix 1953-2003*; retrieved on 10 June 2009 (http://www.ncbe.reading.ac.uk/DNA50/timeline.html).
[20] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 177.

Wilkins maintained that it was helical and shared his opinion on the matter with Watson and Crick. Rosalind likely thought so too, but played the devil's advocate to oppose Wilkins and maintain her position that the X-ray data must prove it, rather than jumping to premature model building. Rosalind teased Wilkins about this by writing a prank obituary and funeral announcement for the DNA helix on July 18th, 1952.[21] Watson and Crick condescendingly told Rosalind that the A-form had to be a helix – she must have made a mistake in her calculations.

Rosalind compiled her data for a report at the end of the year for the Medical Research Council (MRC), which provided the funding for their research. Included were all the dimensions of the DNA unit cell (the smallest repeating unit of the crystal) as well as the respective type of the crystal group to which it belonged. Rosalind had determined that the unit cell of DNA was exactly thirty-four Angstroms in height. This perfectly matched Astbury's prior data – ten bases stacked flat on top of one another, while fitting into one unit cell. The crystal group, which Rosalind assigned to DNA, was based on the unit cell's symmetry – if one flipped it over, it still looked the same. What Rosalind failed to appreciate (which Crick later would), is that the simplest way for DNA to achieve this was for its structure to have two chains running in opposite directions (i.e. anti-parallel). It was already known that DNA chains had directionality (like arrows), and if they pointed the same way, the unit cell would not have the proper symmetry. Meanwhile, Rosalind continued to be unhappy at King's. Due in part to the ongoing conflict with Wilkins she had isolated herself in her lab, not conversing with anyone except Gosling. In June 1952, Rosalind told Randall that she was leaving King's to work with Bernal at Birkbeck College, also in London. As mentioned earlier, Bernal was a prominent and experienced crystallographer, also currently working on large biological molecules. As Rosalind wrote to a friend, "I so much prefer to work under somebody who commands my respect and can offer some encouragement." [22] She obviously felt Wilkins and Randall did not fit this bill. Whether Rosalind decided to leave entirely of her own accord has been debated. Randall certainly knew she was unhappy and at the very least did nothing to try and convince her to stay. Rosalind was scheduled to leave on January 1st, 1953, but eventually stayed until March as she had missed a month of work due to illness.

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[21] Lynn Osman Elkin, "Rosalind Franklin and the Double Helix," *Physics Today* 3 (2003), p. 46.

[22] Brenda Maddox, *Rosalind Franklin: The Dark Lady of DNA* (New York: Harper Collins, 2002), p. 172.

On December 31st, 1952, Linus Pauling and Robert Corey (1897-1971) announced that they had finished their own model of DNA. They had used Astbury's old data with its super-imposed A and B-forms, since Pauling could not obtain any data from Randall. Rosalind had also shown her newer and better X-ray diffraction photos to Corey at a meeting in London, and Corey communicated these findings onto Pauling. At the same time, Linus Pauling's young son Peter had arrived in Cambridge to study in the same lab as Crick, and had also found a friend in his fellow young American, James Watson. Earlier in December, before Pauling and Corey announced their model, word about it had reached Watson and Crick via Peter Pauling. Watson was devastated. They had suspected that Pauling would start working on DNA structure, and feared that he would solve it before them. Unbeknownst to Watson and Crick, Pauling's model was actually very similar to their first try. It also contained three helical chains, with the phosphate backbone again on the inside – and was therefore also incorrect.

Seven Weeks to the Secret: January – March 1953

The younger Pauling asked his father for a copy of the paper, which arrived on January 28th, 1953. Pauling, believing that his model was correct and that he had once again beaten Bragg to the punch, while sending a version of the paper to Bragg as well. Peter showed it to Watson, who immediately recognized that Pauling had made similar mistakes to himself and Crick. Of course Watson was pleased to know that he and Crick had another chance. However, Pauling's model would be published in February, his mistake would be discovered, and he would try again. Watson and Crick thus only had a few weeks head start.

Two days later, Watson came to King's to discuss Pauling's erroneous structure, but had a run-in with Rosalind when he too suggested she did not know how to interpret her X-ray pictures. Instead, Watson ended up commiserating with Wilkins about his poor DNA samples and inability to work with Rosalind. Gosling had just recently shown the beautiful Photograph 51 to Wilkins, which was now already eight months old. As Rosalind was leaving and he had to finish his thesis without supervision, Gosling understandably felt the need to share his work with Wilkins. Wilkins casually showed this picture to Watson during their discussion. Watson, however, had learned much about X-ray crystallography working with Crick since he misunderstood Rosalind's earlier presentation of her results. He immediately recognized the significance of the picture. It was obvious evidence for a helical structure, with clear spacings that made determination of the helix angle and chain separation possible. Watson wrote in his book *The Double Helix*, "The instant I saw the picture, my mouth fell open and my pulse began to race."[23]

The next day, Bragg allowed Watson and Crick to begin building another DNA model. He had his copy of Pauling's report and was not about to allow himself to be beaten again. With Watson's sketch of Rosalind's Photograph 51 in hand, they assembled a model of the B-form. Interestingly enough, Watson again put the phosphates in the center with the bases facing outward, contrary to Rosalind's findings in 1951. Not until Crick insisted that they changed it, did they move the phosphate backbone to the outside. On February 8th, 1953, Watson, Crick, and Peter Pauling met with Wilkins and urged him to start building a model. He said he would as soon as Rosalind had left. Likely feeling guilty for using Rosalind's photograph without her consent, they pressed Wilkins instead to allow them to try model-building again. They failed to mention that they had, in fact, already started to do just that. Wilkins did not like the situation they had put him in, but also disliked confrontation and reluctantly consented. Rosalind in the meantime had been quickly trying to finish up her work at King's before leaving for Birkbeck. She had already accepted that the B-form of DNA must be a two-chain helix, and had calculated many of its dimensions from her Photograph 51. It is clear spacings allowed for calculations determining the angle of the helix, as well as the spacing between the chains. However, she had tried to come up with a structure, which satisfied Chargaff's ratios for the bases, and fit them inside the phosphate backbone as she knew that it was the case.[24] As mentioned earlier, Rosalind did not understand, at that point, that the chains must be anti-parallel to yield the full DNA structure, but she rather focused her research efforts on trying to address the inconsistencies between the A and B-forms, and determine definitively if the A-form was a two chain helix as well. Rosalind and Gosling were also finishing three papers that they planned to publish in *Acta Crystallographica* that spring. These papers summarized what they had learned about DNA so far at King's.

The next week, Max Perutz (1914-2002), a member of the MRC committee and colleague of Watson and Crick's at Cambridge, gave them a copy of Rosalind's as-yet unpublished MRC report from the previous

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[23] James D. Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (New York: Atheneum, 1968), p. 167.

[24] The DNA Riddle: King's College, London. In: NLM, *The Rosalind Franklin Papers* (http://profiles.nlm.nih.gov/ps/retrieve/Narrative/KR/p-nid/187); retrieved on 30 June, 2009.

December. Crick quickly recognized that the symmetry of the DNA unit cell Rosalind described in the report meant that the two chains ran anti-parallel. The symmetry of the DNA unit cell was actually very similar to Crick's own PhD project on haemoglobin. Watson and Crick were nearly there. The only problem that remained was: what held the two chains together? Watson was struggling with this problem in mid-February 1953, trying to decipher how the bases paired up with each other. Another colleague at Cambridge, chemist Jerry Donahue (1920-1985), suggested that he should try a different isomeric form of the bases – the 'keto' form rather than the conventional 'enol.' This change allowed Watson to suddenly realize the base-pairing mechanism: adenine always joined by hydrogen bonds to thymine, and cytosine likewise to guanine. This explained Chargaff's ratios, and also suggested a mechanism for copying the DNA since the strands were complementary to each other. Watson and Crick celebrated at the local pub, where Crick proclaimed, "We have found the secret of life."[25] By March 7th, 1953, the model was complete.

On March 18th, Rosalind heard about Watson and Crick's model, and upon seeing it readily agreed that it looked correct. However, the model did by no means achieve immediate universal acceptance. Although it looked very elegant, Watson and Crick did not have the X-ray photographic evidence to back it up. Rosalind felt that she had the data to prove it. Still, Rosalind left King's for Birkbeck in March 1953, completely unaware that Watson and Crick had used her data to solve the structure. On April 25th 1953, Watson and Crick's model was published in the premier scientific journal *Nature*. They acknowledged that their model was as yet unproven, and that Rosalind's accompanying article may help to prove their model's assumptions. But they only cited "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."[26] Given that Watson had seen Rosalind's Photograph 51, and they both had seen her MRC report, biologist and historian of science Lynn Elkin writes:

> That oblique acknowledgement misrepresented Franklin's role and, whatever its intentions, left most people with the impression that her work

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[25] Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*, p. 197.

[26] James D. Watson, Francis H.C. Crick, "A Structure for Deoxyribose Nucleic Acid," *Nature* 171 (1953), pp. 737-738.

mainly served to confirm that of Watson and Crick. It has to be one of the greatest understatements in the history of scientific writing.[27]

Birkbeck College and Tobacco Mosaic Virus

At Birkbeck College, Rosalind worked on the structure of a plant virus – the Tobacco Mosaic Virus – again using X-ray crystallography technique. She led a research team including Aaron Klug (b. 1926) and two research assistants. Together they made great strides in understanding the TM virus. In 1955, Franklin published an article in Nature in which she showed that individual TM viruses were all exactly of the same length.[28] This was in direct contradiction to the prominent British virologist Norman Pirie (1907-1997), but her results were correct. While at Birkbeck, Rosalind was also invited to speak in the United States on her coal research, which she had done in Paris several years earlier. Despite being out of that field for several years, she was still considered a world expert on carbon structures; she made trips to the United States to speak at conferences in 1954 and 1956. This also allowed her to establish and maintain relationships with virology researchers in the USA. One of these contacts, Wendell Stanley (1904-1971) would later call Rosalind an "international courier of good will and scientific information".[29] Rosalind's five years at Birkbeck College were the most productive of her academic career – she and Klug published seventeen papers in that time. She became a well-known and respected researcher around the world, and thrived in spite of the opposition from her famous colleague, the British biochemist Norman Pirie (1907-1997).

During Rosalind's second trip to the United States in 1956, she developed abdominal pain and swelling; and upon her return to England in August, she was diagnosed with ovarian cancer. Rosalind continued her research in 1957 even between surgeries and chemotherapy treatments and obtained another three-year research grant, ensuring that her research team could continue after she had passed away. In March 1957, Rosalind was readmitted to the hospital, and she died on April 16th at the age of thirty-seven.

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27 Elkin, *Rosalind Franklin and the Double Helix*, p. 46.

28 Rosalind E. Franklin, "Structure of Tobacco Mosaic Virus," *Nature* 175 (1955), pp. 379-381.

29 The DNA Riddle: King's College, London. In: NLM, *The Rosalind Franklin Papers* (http://profiles.nlm.nih.gov/ps/retrieve/Narrative/KR/p-nid/187); retrieved on 30 June, 2009.

Rosalind Forgotten and Remembered

In 1962, James Watson, Francis Crick, and Maurice Wilkins were awarded the Nobel Prize in Physiology or Medicine for their work on DNA and RNA. Rosalind was ineligible to receive the prize, as the prize could not be awarded posthumously. Aaron Klug stated upon receiving his own prize in 1982 that "had [Rosalind's] life not been cut tragically short, she might well have stood in this place on an earlier occasion."[30] The 1962 prize would have been an opportunity for one of the three to give Rosalind credit for making their discovery possible. Neither Watson nor Crick made any mention of her, and Wilkins only briefly. According to Wilkins, Crick asked him to speak about her, so it seems at least he recognized it should be done.[31]

Watson published his famous autobiography *The Double Helix* in 1968. The book was extremely popular among the public, but surrounded by controversy in the academic community. Wilkins and Crick both had objections to the way Watson portrayed Rosalind and themselves. Several others (including Pauling, Perutz, and Rosalind's siblings), voiced their objections to his book. This eventually convinced Harvard University Press to drop it, and compelled Watson to publish it privately instead. Wilkins declared that the book was "unfair to me, Dr. Crick and to almost everyone mentioned except Professor Watson himself."[32] In his book, Watson finally admitted that he and Crick had seen Rosalind's research and that it was fundamental to their completion of the DNA model. However, Watson explained his actions away with dismissive comments and a crass portrayal of 'Rosy' as he called her. He continued to defend his actions for decades at academic gatherings around the world. This mistreatment was "sufficient to launch the legend of Franklin as the 'wronged heroine'".[33]

Klug wrote a forceful counter to Watson's book in Nature[34], and an outraged crystallography community convinced Rosalind's good friend, the newsletter editor Anne Sayre (1923-1978) to write a biography of her

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[30] Aaron Klug, *From Macromolecules to Biological Assemblies* (Nobel Lecture, Stockholm, Sweden, December 8, 1982).
[31] Elkin, *Rosalind Franklin and the Double Helix*, p. 47.
[32] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 312.
[33] *Ibid*., p. 407.
[34] Aaron Klug, "Rosalind Franklin and the Discovery of the Structure of DNA," *Nature* 218 (1968), pp. 808-810 and pp. 843-844.

as well.[35] Sayre's book was a vast improvement over Watson's in terms of historical accuracy; however, it had been influenced by the feminist opinions of the day. As a result, Rosalind's failure to receive the Nobel Prize was viewed for many years as a prime example of the mistreatment of women in science, rather than a consequence of the Nobel Prize rules. Brenda Maddox sought to write a more unbiased biography of Rosalind Franklin for the 50th anniversary of the discovery of DNA; her book does not gloss over the less attractive features of Rosalind's personality and accurately portrays the events leading up to the discovery of the double helical structure of DNA in 1953. Maddox recognizes that class, religion, and ethnicity were probably bigger obstacles to Rosalind's scientific career than gender.[36]

Discussion

The magnitude of Rosalind's contributions to the discovery of the structure of DNA should now be evident. Rosalind first recognized that DNA had two forms – A and B – and characterized conditions to interchange between them. Rosalind also deduced from her experiments that the sugar-phosphate backbone had to be on the outside of the molecule. Finally, she did much of the mathematical work on her diffraction pictures which defined the dimensions and symmetry of the structure. As shown above, Watson and Crick largely based their model on her MRC report and Watson's sketch of her famous photograph number fifty-one.[37]

How close Rosalind came to discovering the structure by herself can be seen by examining a draft of Rosalind's Nature article, dated March 17th, 1953 – one day before she saw Watson and Crick's model.[38] She had correctly decided that both the A and B-forms must be double helices, and that the chains must be anti-parallel in the A-form. Likely, she would have soon concluded that the chains were anti-parallel in the B-form as well. The final step would then have been to discover the base-pairing mechanism. Rosalind's notebook shows that she was considering Chargaff's ratios, and how the bases' hydrogen atoms bond to each other. The base-pairing step is a giant leap of intuition that Watson should

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35 Anne Sayre, *Rosalind Franklin and DNA* (New York: WW Norton and Co., 1975).

36 Robert P. Crease, "The Rosalind Franklin Question," *Physics World* 3 (2003), p. 17.

37 *Ibid.*, p. 17.

38 Klug, *Rosalind Franklin and the Double Helix*, p. 787.

receive credit for, but it is noteworthy that Watson did not make this discovery until shown the alternative isomeric forms of the bases by his colleague Jerry Donahue. Rosalind, in contrast, was working in near complete isolation. Why did Watson and Crick not simply give Rosalind credit for her work in their *Nature* article? A probable explanation was because they would have had to explain how they came across her unpublished results. Also, it would become obvious that they had been quietly working, as Watson himself put it, "on the problem of a close friend."[39] There is no evidence that Watson or Crick ever told Rosalind that they had used her data – she perhaps even died not knowing.

Despite Watson and Crick's lack of citation of Rosalind's work, it is remarkable that the scientific community did not appreciate her efforts until many years after her death. There are several reasons for this. For one, Rosalind's paper appeared below Watson's and Crick's in *Nature* in April 1953, seemingly only in support of their model. Had Watson and Crick properly cited Rosalind's data – and the papers appeared in the reverse order – the result may have been accurate: Watson and Crick's model derived from Rosalind's proof. Also, very few outside the X-ray crystallography community understood the biological significance of the mathematical work Rosalind had done. Finally, the importance of Watson's and Crick's model was not wholly recognized by the wider scientific community until Rosalind had already died. Not until Watson's 1968 autobiography was countered by Aaron Klug and Anne Sayre did the Rosalind Franklin story come to light.

Conclusions

In the modern scientific community, Rosalind Franklin's contributions to the discovery of DNA are well recognized.[40] Many maintain that questionable behaviour such as Watson and Crick's is still not uncommon among scientists. But in part due to accounts like Rosalind's, the sensitivity of the present academic community and the general public is heightened to unfair play. The magnitude of the discovery of DNA and the untimely circumstances of her death are also no doubt contributing factors to the fame of Rosalind's story.

However, she is no longer simply labelled as a 'wronged heroine', which Maddox says "overshadowed her intellectual strength and

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[39] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 177.
[40] Crease, *The Rosalind Franklin Question*, p. 17.

independence both as a scientist and as an individual".[41] As Maddox wrote in a letter to her father from Cambridge, Rosalind gave her best to science in order to "improve the lot of mankind, present and future."[42] Rosalind's story can be remembered as a negative example of academic dishonesty and the difficulties and challenges that women faced in science. However, Rosalind can also be remembered positively as an excellent researcher and contributor to science. Her work on DNA, as well as her prior work on carbon structures and subsequent work on viruses, were invaluable contributions to the fields of chemistry, biology, and medicine. Indeed, her perseverance has paid dividends many times over for the generations that followed her. The Irish biophysicist John Desmond Bernal (1901-1971) accurately summed up her life as a scientist in her obituary in a *Nature* article in 1958:

> As a scientist Miss Franklin was distinguished by extreme clarity and perfection in everything she undertook. Her photographs are among the most beautiful X-ray photographs of any substance ever taken. Her devotion to research showed itself at its finest in the last months of her life. Although stricken with an illness which she knew would be fatal, she continued to work right up to the end. Her early death is a great loss to science.[43]

[41] Maddox, *Rosalind Franklin: The Dark Lady of DNA*, p. 407.
[42] *Ibid*., p. 61.
[43] John Desmond Bernal, "Dr. Rosalind E. Franklin," *Nature* 182 (1958), p. 154.