The Secret Lives of DNA

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Unravelling the Double Helix: The Lost Heroes of DNA
by Gareth Williams
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DNA first came to the public's attention in 1953 when, as James Watson later claimed, Francis Crick "winged into The Eagle to tell everyone within hearing distance" that the two of them had discovered the secret of life.[1] This secret was the double helical structure of DNA. The discovery was an achievement in its own right, but it should not be conflated with either the discovery of DNA itself or the discovery of its function as the material carrier of life's instructions.[2] These discoveries were made eighty-five and nine years earlier, respectively. Without knowledge of the existence of DNA and its vital function, no one would have thought to tackle the problem of its structure.

In *Unravelling the Double Helix*, Gareth Williams details the way in which Watson and Crick came up with their double-helix model only in the last quarter or so of his book, which comprises twenty-six chapters running to nearly 500 pages. The first three-quarters of the book traces the stories of several scientists from the mid-nineteenth century onward.[3] All these people were, in one way or another, involved in some aspect of research on DNA and "were variously enthralled, seduced or infuriated" by it.[4]

In a chapter aptly titled "In the Beginning," Williams describes the first seduction enacted by DNA.[5] It began in 1868, in a venue apropos for romance: a medieval castle in the German town of Tübingen. But any romantic images dissipate upon learning what went on inside. The castle had been acquired by the University of Tübingen in the 1830s, and during the icy winter of 1868, in an unheated laboratory occupying the space of its former kitchens, a young Swiss student named Friedrich Miescher was painstakingly washing pus off surgical bandages obtained from a nearby hospital.

Why pus? Unlikely as it may now seem, pus was the most easily obtainable and abundant source of the cells Miescher needed for his investigations. His intention in coming to Tübingen had been to study the chemical composition of cells under the pioneering physiological chemist Felix Hoppe-Seyler, best known for coining the name hemoglobin.[6] Hoppe-Seyler steered Miescher toward white blood cells (leucocytes) as the best source material for his studies of cell chemistry. A nearby surgical clinic provided a steady supply of surgical bandages, the pus in which yielded sufficient quantities of leucocytes for his experiments.[7] From these cells, Miescher extracted a phosphate-rich substance that seemed distinct from other substances such as proteins, lecithins, and the products of their breakdown.[8] He called this new material *nuclein*, the substance we now recognize as DNA, for its specific location in the cells' nuclei.

There was nothing easy about Miescher's work, as Williams makes clear with vivid descriptions of the tasks at hand: comparing, for instance, the extraction of nuclei from the leucocytes to "pitting cherries less than one-thousandth of their usual size."[9] It took Miescher about a year to conduct his analyses and produce sufficient data to submit his write-up to Hoppe-Seyler. The latter was at first suspicious of Miescher's conclusions regarding the uniqueness of nuclein. Hoppe-Seyler did not immediately publish the paper. Instead he waited nearly two years, repeating Miescher's experiments himself and assigning further investigations to another of his students. The results of these experiments convinced him so thoroughly that when Miescher's paper was eventually published, Hoppe-Seyler contributed an introduction. He freely admitted his own prior reservations, before going on to offer fulsome praise: "When I turn to describing the results of these investigations, I can only emphasize that, insofar as I have checked Miescher's information, they must be considered as being fully confirmed."[10]

Williams describes Miescher's initial discovery as a "revelation that fell like a bolt from the blue into a mind that was totally unprepared, because this was the very beginning and, as with the Big Bang, nothing existed before this moment."[11] For an unprepared mind, Miescher proved remarkably prescient about the significance of his discovery. He speculated that the nucleins constituted an entire family of phosphorus-containing substances, whose role in effecting cellular functions would prove equal in importance to that of proteins. He also predicted that, "understanding the relationships between nuclear materials, proteins, and their metabolic products will gradually help to lift the veil, which still so completely obscures the internal processes of cell growth."[12]

In the third and fourth chapters of *Unravelling the Double Helix*, Williams describes several other origin stories. Landmarks include the first description of the cell's nucleus as a distinct entity by the British botanist Robert Brown in 1833;[13] the German anatomist Walther Flemming's microscopic studies of cell division and his speculations that chromatin—a term he coined—was identical to Miescher's nuclein;[14] and Gregor Mendel's famed experiments on the hybridization of pea plants, which allowed him to lay out the fundamental principles of the inheritance of various traits.[15] Mendel's presence in this roster might seem somewhat incongruous. In contrast to Miescher, Brown, and Flemming, Mendel's name is well-known among scientists and historians, and to a lesser extent among the broader public. But initially, Mendel's contributions were unsung. Save for certain specialist references to his 1866 work, it was not until 1900 that three botanists in Germany and the Netherlands published papers describing his findings and their significance.[16]

Rather than going into the hybridization experiments, Williams begins chapter 4 in the summer of 1878, when C. W. Eichling, a young German traveling salesman of botanical novelties, spent a day at the monastery in Brünn where Mendel lived and maintained his garden. At an earlier stop in Erfurt, Eichling, whose trip combined "propaganda and [industrial] espionage," had learned of Mendel quite by chance from a plant merchant, Ernst Benary.[17] Since Brünn was on his itinerary, Eichling followed up on Benary's lead and paid a visit to this "'prominent academic customer' who had done … some strange experiments by peas." Although Eichling and Mendel spent considerable time together as they walked in the abbey's garden where the hybridization experiments had taken place, peas do not seem to have figured prominently in the conversation. Except for mentioning to Eichling that he had "'reshaped' the peas to serve the abbey 'to better advantage,'" Mendel proved reticent on the details when questioned further, saying only that it was too long a story and changing the subject. Decades later, Eichling admitted that

> by failing to draw the master out with a sympathetic question I missed a priceless chance, in that garden sixty-four summers ago, to hear from the lips of the founder of Genetics how he made the discovery which today is recognized as marking an epoch in the study of life.[18]

Not all the stories Williams tells are as pleasant as Eichling's meeting with Mendel. Particularly poignant is the account of the Russian botanist and pioneer of wheat genetics, Nikolai Vavilov. A target of the infamous Lysenko affair, Vavilov suffered a truly harrowing end. "His gravest error," Williams observes, "was to be a man of principle."[19] For his pursuit of Mendelian genetics and evidence-based science, Vavilov earned Trofim Lysenko's enmity and was arrested in 1940 by the Soviet secret police while on a plant-collecting expedition. A 1945 obituary in *Nature* speculated about his fate: "News has recently been received of the death in the Soviet Union of Nikolai Ivanovich Vavilov. The circumstances are not precisely known, but the time was after December 1941 and the place probably Saratov."[20]

It was not until 1965, when the USSR Academy of Sciences launched an investigation, that the full story of Vavilov's end came to light.[21] Mark Popovskii, a science journalist who took part in the investigation, faced KGB harassment and had to smuggle material out of the country before finally publishing a biography of Vavilov in 1984.[22] "After 400 sessions of interrogation, some lasting thirteen hours, to make him confess to being an English spy sent to destroy Soviet agriculture," Vavilov's fate was decided at a ten-minute trial. He was deemed guilty of being a saboteur and spy, and sentenced to twenty years' imprisonment.[23] Vavilov took ill and died in a prison hospital in Saratov in January 1943, but not before boosting his fellow prisoners' morale by delivering whispered lectures on science, agriculture, and trees.[24]

In the many strands of DNA's secret life, Williams points out that there are only two instances in which scientists "broke entirely new ground." Otherwise, every actor in this book "had something already established to work on."[25] The first, of course, was Miescher. The second was the English bacteriologist and public health officer Frederick Griffith. His 1927 discovery initiated a line of investigation culminating in what was perhaps the most important breakthrough for twentieth-century biology. Williams described Griffith's contribution as a discovery which "lit a slow-burning fuse that, twenty-five years later, detonated the biggest bang of twentieth-century biology."[26]

In Griffith's case, as in Miescher's, the saga began with a similarly unlikely and obscure source of DNA: small, spherical bacteria called pneumococci, which cause pneumonia. Griffith was a specialist in mapping various infections, and, while examining specimens of lobar pneumonia in the early 1920s, he encountered an odd phenomenon. Rather than just one single antigenic type or strain of pneumococcus, he found more than one type in the same patient, appearing several days after the infection took place.[27] Considering it unlikely that the patients could be suffering from multiple infections, he posited that all the later-appearing types were derived from the initial pneumococcal type and devised a series of experiments to test his idea.[28] These experiments led to his groundbreaking discovery of bacterial transformation: the ability of a live avirulent, meaning noninfectious, pneumococcal type to transform into a virulent type when injected into a mouse together with a heat-killed virulent pneumococcus.[29] The specificity of the transformed type always matched the dead strain used in the experiment.

What was the reason one pneumococcal type transformed into another? The difference in virulence between the different types of virulent pneumococci was mapped easily enough to the chemical makeup and antigenic properties of the bacterial capsules. Avirulent strains of bacteria lacked a capsule altogether. But scientists found the capsules could not, by themselves, induce the bacteria to transform; something else was controlling which capsular antigen was produced. This something else, dubbed the "transforming principle," took more than a dozen years of intermittent work to find. Most of it was conducted in the laboratory of the bacteriologist Oswald Avery at the Rockefeller Institute for Medical Research. These efforts culminated in 1944, with a paper that stopped just shy of announcing that the DNA-containing transforming principle was a gene: "The evidence presented supports the belief that a nucleic acid of the desoxyribose type is the fundamental unit of the transforming principle of Pneumococcus Type III."[30]

Those dozen years from Griffith to Avery, as well as the aftermath, are covered ably by Williams, and readers may consult other accounts for further details and insights into the discovery and its reception.[31] I would like to mention the work of the junior member of Avery's team, Maclyn McCarty, whose follow-up contribution merits him a place among the lost heroes of DNA.[32] It was McCarty who designed the experiments that clinched the evidence for DNA's role in pneumococcal transformation. With simple expediency, his experiments compared the transformative abilities of pneumococci when subjected to treatment by enzymes that specifically degraded proteins, DNA, or RNA.[33] Only the enzyme DNase, degrading DNA, could inactivate the transforming principle. But even this evidence that DNA was key failed to attract sufficient notice. Avery's Rockefeller colleague Alfred Mirsky was strongly opposed to his ideas, and the unfortunate consequence was that other biologists were slow to accept DNA as the material of heredity.[34]

Williams begins *Unravelling the Double Helix* with a glimpse of the end point before narrating the events that led up to it. I end this review by drawing attention to the book's beginning, namely the material that prefaces the narrative. It includes a five-page timeline and an eight-page cast of the major investigators whose work is described in the book.[35] Both are useful features for a tale as long as this one. There is also a preface, in which Williams describes his motives for embarking on this particular project: "ignorance, curiosity and a couple of chance encounters."[36]

In the epigraph, Williams cites Rosalind Franklin. In 1953, upon hearing that Watson and Crick had deduced the double helical structure of DNA, Franklin apparently reacted by paraphrasing Sir Isaac Newton: "We all stand on each other's shoulders."[37] Although Newton's statement has come to represent the importance of giving credit to one's predecessors, or as Williams puts it, "ancestor worship" of a sort,[38] it may not have been as gracious as it seems. Newton alluded to the shoulders of giants in a letter to Robert Hooke, with whom he had a rather fractious relationship over, among other things, priorities in certain discoveries. The statement has been interpreted by some as a sarcastic dig by the upper-class Newton at his lower-class rival's diminutive stature and deformity—Hooke suffered from a humpback.[39] My thought on reading the epigraph was to wonder if Franklin was aware of the intended irony in Newton's statement. If she was in fact aware of the barb, her allusion to it is all the more ironic because of her own openly difficult relationship with Maurice Wilkins, who had, without her permission, shared with Watson her crucial X-ray photograph that led them to propose DNA's helical structure.[40] It is tempting to wonder whether Franklin considered herself the intellectually superior Newton to Wilkins's Hooke.

Unravelling is so sprawling, and its cast of characters so wide, that it would be easy to write several reviews focusing on different episodes and figures than I have here. It is not a book to be read in a single sitting, but it needs to be read from beginning to end, at least the first time around, otherwise the reader could become quickly lost. It is to Williams's credit that he retains control of all the narrative threads without ever getting himself or the readers hopelessly entangled.[41] He found a good story, or rather many stories, and got about the business of telling them.

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1. James Watson, *The Double Helix: A Personal Account of the Discovery of the Structure of DNA* (New York: Simon & Schuster; London: Weidenfeld & Nicolson, 1968), 235.
2. Friedrich Miescher, "Über die chemische Zusammensetzung der Eiterzellen (On the Chemical Composition of Pus Cells)," *Medicinisch-chemische Untersuchungen* 4 (1871): 441–60; Oswald Avery, Colin MacLeod, and Maclyn McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III," *The Jour-*

nal of Experimental Medicine 79 (1944): 137–58, doi:10.1084/jem.79.2.137.

3. Gareth Williams, *Unravelling the Double Helix: The Lost Heroes of DNA* (London: Weidenfeld & Nicolson, 2019).
4. Williams, *Unravelling the Double Helix*, xxvi.
5. Williams, *Unravelling the Double Helix*, 9–22.
6. Felix Hoppe, "Über das Verhalten des Blutfarbstoffes im Spectrum des Sonnenlichtes (On the Behavior of Blood Pigments in the Spectrum of Sunlight)," *Virchows Archiv* 23 (1862): 446–49, doi:10.1007/bf01939277; Felix Hoppe-Seyler, "Über die chemischen und optischen Eigenschaften des Blutfarbstoffs (On the Chemical and Optical Properties of Blood Pigments)," *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin* 29 (1864): 597–600, doi:10.1007/bf01926067. Note: Orphaned at a relatively young age, Hoppe-Seyler attached the name Seyler to his family name, Hoppe, in 1864 when he was formally adopted by his brother-in-law Georg Seyler.
7. Ralf Dahm, "The First Discovery of DNA," *American Scientist* 96, no. 4 (2008): 320, doi:10.1511/2008.73.320.
8. Miescher, "Über die chemische Zusammensetzung der Eiterzellen."
9. Williams, *Unravelling the Double Helix*, 12.
10. Felix Hoppe-Seyler, "Über die Chemische Zusammensetzung des Eiters (On the Chemical Composition of Pus)," *Medicinisch-Chemische Untersuchungen* 4 (1871): 486 (translation courtesy of Kersten Hall).
11. Williams, *Unravelling the Double Helix*, 8.
12. Miescher, "Über die chemische Zusammensetzung der Eiterzellen," 459–60. A complete scholarly translation of Miescher's original contribution, together with a contextualizing commentary is now available: Kersten Hall and Neeraja Sankaran, "DNA Translated: Friedrich Miescher's Discovery of Nuclein in Its Original Context," *British Journal for the History of Science* 54 (2021): 99–107, doi:10.1017/S000708742000062X.
13. Williams, *Unravelling the Double Helix*, 24–26; Robert Brown, "On the Organs and Mode of Fecundation in *Orchideæ* and *Asclepiadeæ*, with Additional Observations," *Transactions of the Linnean Society of London* 16 (1833): 685–745, doi:10.1017/cbo9781107775473.017.
14. Williams, *Unravelling the Double Helix*, 28–35; Walther Flemming, *Zellsubstanz, Kern und Zeillteilung* (Cell Substance, Nucleus, and Cell Division) (Leipzig: Vogel, 1882).
15. Williams, *Unravelling the Double Helix*, 36–51; Gregor Mendel, "Versuche über Pflanzenhybriden (Experiments on Plant Hybridization)," *Verhandlungen des naturforschenden Vereines in Brünn*, Bd. IV für das Jahr 1865 (1866).
16. Robert Olby and Peter Gautrey, "Eleven References to Mendel before 1900," *Annals of Science* 24 (1968): 7–20, doi:10.1080/00033796800200021. The three publications marking the rediscovery of Mendel are Carl Correns, "G. Mendel's Regel über das Verhalten der Nachkommenschaft der Rassenbastarde (Mendel's Law on the Behavior of Progeny of Variable Hybrids)," *Berichte der Deutschen Botanischen Gesellschaft* 18 (1900): 156–68, doi:10.1007/978-3-642-52587-2_2; Hugo de Vries, "Sur la loi de disjonction des hybrides (On the Law of Hybrid Disjunction)," *Comptes Rendus de l'Academie des Sciences* 130 (1900): 845–47; and Erich von Tschermak, "Über künstliche kreuzung bei *Pisum sativum* (On the Artificial Crossing of *Pisum sativum*)," *Berichte der Deutschen Botanischen Gesellschaft* 18 (1900): 232–39.
17. Williams, *Unravelling the Double Helix*, 36–38.
18. C. W. Eichling, "I Talked with Mendel," *Journal of Heredity* 33 (1942): 246, doi:10.1093/oxfordjournals.jhered.a105181.
19. Williams, *Unravelling the Double Helix*, 171.
20. Sydney Harland and Cyril Darlington, "Prof. N. I. Vavilov, For.Mem.R.S.," *Nature* 156 (1945): 621, doi:10.1038/156621a0.
21. Allan Wilson, "Review: *The Vavilov Affair* by Mark Popovsky," *New Zealand Slavonic Journal* (1987): 246–49.
22. Wilson, "Review: *The Vavilov Affair*," 246–47; Mark Popovskii, *The Vavilov Affair* (Hamden: Archon Books, 1984).
23. Williams, *Unravelling the Double Helix*, 231.
24. Williams, *Unravelling the Double Helix*, 232; John Fincham, "The Fall of Nikolai Vavilov," *Nature* 316 (1985): 769–70, doi:10.1038/316769a0.
25. Williams, *Unravelling the Double Helix*, 372.
26. Williams, *Unravelling the Double Helix*, 138.
27. Frederick Griffith, "Types of Pneumococci Obtained from Cases of Lobar Pneumonia," *Reports on Public Health and Medical Subjects* 13 (1922): 1–13.
28. There is no need to rehash the details of Griffith's experiments to test his idea. Readers may find them not only in Williams's beautifully clear account and other historical treatments, but also in Griffith's own publications. Williams, *Unravelling the Double Helix*, 138–42; Pierre-Olivier Méthot, "Bacterial Transformation and the Origins of Epidemics in the Interwar Period: The Epidemiological Significance of Fred Griffith's 'Transforming Experiment'," *Journal of the History of Biology* 49 (2016): 311–58, doi:10.1007/s10739-015-9415-6; Frederick Griffith, "The Significance of Pneumococcal Types," *Journal of Hygiene* 27, no. 2 (1928): 113–59, doi:10.1017/s0022172400031879.
29. Griffith, "Significance of Pneumococcal Types."
30. Avery, MacLeod, and McCarty, "Studies on the Chemical Nature," 156. Note: The phrase "nucleic acid of the desoxyribose type" stands for DNA. The term "desoxyribose" has since been completely replaced by the more familiar "deoxyribose" which denotes the D in DNA (deoxyribonucleic acid).
31. Williams, *Unravelling the Double Helix*, 143–53; Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology* (New York: Simon and Schuster, 1979); Lewis Thomas, "Oswald Avery and the Cascade of Surprises," *Technology in Society* 6, no. 1 (1984): 37–40, doi:10.1016/0160-791X(84)90016-2; Nicholas Russell, "Oswald Avery and the Origin of Molecular Biology," *British Journal for the History of Science* 21, no. 4 (1988): 393–400, doi:10.1017/S0007087400025310; Olga Amsterdamska, "From Pneu-

monia to DNA: The Research Career of Oswald T. Avery," *Historical Studies in the Physical and Biological Sciences* 24, no. 1 (1993): 1–40, doi:10.2307/27757711; Robert Olby, *The Path to the Double Helix: The Discovery of DNA* (Mineola: Courier Dover Publications, 1994); F. Kohl, "Konzepte und Experimente zum Nachweis der DNA als Vererbungssubstanz: Der historische Weg von Mendel und Miescher zum Schlüsselversuch der Avery-Gruppe und dessen Bestätigung am Phagenmodell (The Concepts and Experiments to Demonstrate DNA as the Substance of Heredity: The Historical Path of Mendel and Miescher to the Key Experiment of the Avery Group and Its Confirmation in the Phage Model)," *Deutsche medizinische Wochenschrift* (1946) 121, no. 34/35 (1996): 1,066–69, doi:10.1055/s-0029-1233824; Ute Deichmann, "Early Responses to Avery et al.'s Paper on DNA as Hereditary Material," *Historical Studies in the Physical and Biological Sciences* 34, no. 2 (2004): 207–32.

32. McCarty's achievements deserve wider recognition for their scientific merit alone, but it should be added that he also qualifies for the label that Williams bestowed upon Walther Flemming, as "one of the few genuinely nice people in the history of DNA." Williams, *Unravelling the Double Helix*, 29. I can attest to this same quality in Mac McCarty, whom I met with and interviewed a few times in 1996 and 1997, more than half a century after he had performed the transformation experiments.
33. Maclyn McCarty and Oswald Avery, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types," *Journal of Experimental Medicine* 83 (1946): 89–96, doi:10.1084/jem.83.2.89; Maclyn McCarty, "Chemical Nature and Biological Specificity of the Substance Inducing Transformation of Pneumococcal Types," *Bacteriological Reviews* 10 (1946): 63–71, doi:10.1128/br.10.1-2.63-71.1946.
34. Williams, *Unravelling the Double Helix*, 217.
35. Williams, *Unravelling the Double Helix*, xiii–xvii and xviii–xxv.
36. Williams, *Unravelling the Double Helix*, xxvi–xxx.
37. Williams, *Unravelling the Double Helix*, ix.
38. Williams, *Unravelling the Double Helix*, xxviii.
39. Robert Crease, *The Great Equations: Breakthroughs in Science from Pythagoras to Heisenberg* (New York: W. W. Norton & Company, 2010, Kindle Edition), 82.
40. Williams, *Unravelling the Double Helix*, 8, 327–29.
41. Although writing is not Williams's primary profession, *Unravelling* is by no means his first book; he has written others about aspects of the history of medicine and disease, and is the author of a delightful book about the Loch Ness monster. Gareth Williams, *A Monstrous Commotion: The Mysteries of Loch Ness* (London: Orion Books, 2015).

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