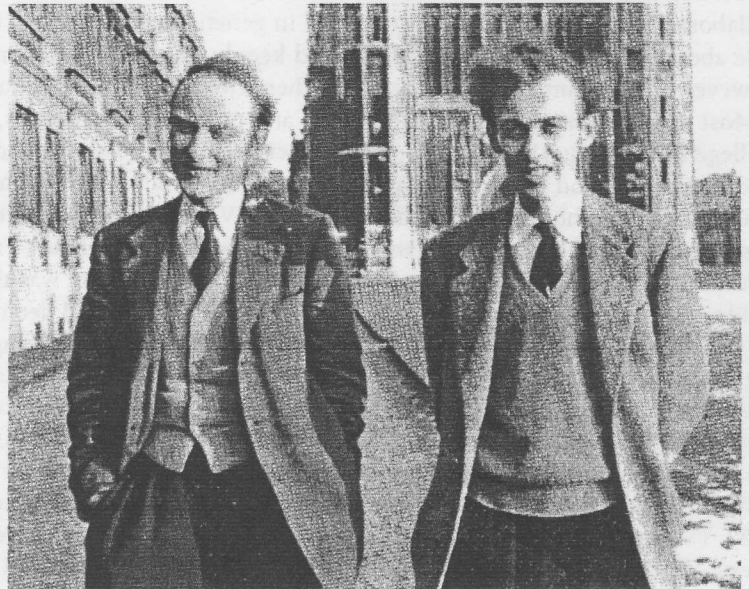


# Envisioning DNA: The Nature of Science and the Search for the Double Helix

by *Stephen Pasquale*

Science is a distinct and uniquely human way of learning about the world. As a process, science is distinguished from other ways of knowing by strict reliance on empirical data, logical argument, rules of evidence, skepticism, and testable explanations that lead to accurate predictions. As humans, scientists collaborate and compete with one another, and they are influenced in varying degrees by ethical traditions, societal and cultural norms, as well as personal beliefs and ambitions. The history of science recounts many tales of discovery that exemplify these attributes. In biology, the search for the structure of DNA stands as one of the most memorable of such episodes.

When 23-year-old James Watson and 35-year-old Francis Crick met for the first time at Cambridge University's Cavendish Laboratory in 1951, almost 90 years had elapsed since the German biologist Haeckel first proposed that the cell nucleus contained all of the "factors" necessary for the transmission of hereditary information. It had also been half a century since the rediscovery of Mendel's laws implying the particulate nature of the gene. During the first half of the



Watson and Crick  
(Cold Spring Harbor University Archives)

twentieth century, work by geneticists and cytologists had transformed scientists' understandings of the gene from a purely hypothetical construct into a chemical entity located in the chromosomes. Genes had been experimentally mutated using x-rays and mapped along chromosomes as if they were strung out like beads on a string.

Still, in 1951, there was no consensus among scientists as to the chemical nature of the gene or its three-dimensional structure. Chromosomes were known to contain almost equal masses of protein and deoxyribose nucleic acid, or DNA. Most scientists at the time assumed that the proteins, because of their variety and versatility, were the most likely candidates for the molecule of heredity. DNA's limited repertoire of nucleotide subunits, each containing phosphorous, deoxyribose sugar, and one of four organic bases—adenine, guanine, cytosine, or thymine—caused it to be widely viewed as a boringly repetitive scaffold (TGAC TGAC ...) that supported the supposedly information-encoding and self-replicating proteins.

Jim Watson, in 1951, a newly-minted Ph.D. pursuing postdoctoral study at Cambridge, had become interested in the chemical nature of the gene during his graduate studies with the physicist-turned-biologist Salvadore Luria. During summers, Luria had taken Watson to Cold Spring Harbor Laboratory on Long Island to interact with members of the so-called "phage group." This small band of physicist-biologists was keenly interested in the genetics of bacteriophage, the viruses that infect bacteria, and they helped to shape young Jim's scientific interests. These scientists were very aware of the history of genetics, as well as recent experiments that strongly suggested that the gene was in fact made of DNA. In 1944, Oswald Avery, Colin Macleod, and Maclyn McCarty at Rockefeller University had demonstrated that the so-called "transforming principle" (a chemical component of virulent pneumococcal bacteria that can convert harmless strains into disease-producing cells) is not made of protein, polysaccharide, or fat. The only thing left was DNA.

But strong opinion dies hard. Skeptics of DNA continued to believe that the genetics of bacteria was atypical, and that the genes of more complex cells were made of protein. It was not until 1952 that phage geneticists Alfred Hershey and Martha Chase conducted the key experiment that turned the weight of evidence in favor of DNA. Their so-called "Waring Blender Experiment" clearly demonstrated that it was the phage's DNA, not its protein, that enters the infected bacterium to direct the production of genetically identical new phage.

Watson and Crick were already convinced in the fall of 1951 that DNA was the key. For them, three big questions loomed: What was the structure of DNA? How did it replicate? How did it encode proteins? They appreciated that a successful attack on the puzzle of DNA structure required an integrated, interdisciplinary approach—one that employed more than one technique and also accounted for relevant chemical and physical data. Thanks to prior efforts of several scientists, some information was already at hand: DNA had a backbone of linked sugar and phosphate groups; the four organic bases fell into two classes, double-ringed purines and single-ringed pyrimidines; and the bases were oriented at a right angle to the sugar-phosphate backbone.

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Another key piece of evidence had been provided just the year before by the biochemist Erwin Chargaff. According to "Chargaff's Ratios," the amount of adenine in any DNA sample always equals the amount of thymine ( $A = T$ ), and the amount of guanine equals that of cytosine ( $G = C$ ). Further, each species' DNA appeared to have a unique ratio of  $A + T$  to  $C + G$ . For Watson and Crick, this evidence logically implied that the prevailing view of DNA's base sequence as a simple repetitive pattern of the type TGAC TGAC ... was wrong. The bases must occur instead in a varied sequence to encode genetic information.

Watson and Crick's approach over a period of 16 months to the puzzle of DNA structure clearly exemplifies the roles of collaboration and competition in scientific research. For example, each researcher brought different training and interests to their collaboration—Watson, a biologist trained in genetics and interested in experimentation, and Crick, a physicist knowledgeable about x-ray diffraction technology and keenly interested in theory. Neither had experience working with purified DNA, however. This meant collaborating with other scientists with the requisite expertise and interest in DNA.

Most notable among these collaborators, and potential competitors, were Maurice Wilkins and Rosalind Franklin of King's College in London. They were expert x-ray crystallographers who had been working for about a year on the structure of DNA. The Cambridge and London groups informally shared ideas and certain aspects of their data. It was actually Rosalind Franklin's x-ray photos of DNA that convinced Watson and Crick as early as the fall of 1951 that DNA must be a helix. In a classic example of how scientists can interpret the same data differently, Franklin herself temporarily abandoned the idea of a helix.

Another formidable competitor in the race for DNA structure was the Nobel Prize-winning chemist Linus Pauling of the California Institute of Technology. Earlier that year, Pauling had determined the first three-dimensional structure of a biological macromolecule, the  $\alpha$ -helix of protein. Watson and Crick were impressed by Pauling's use of multiple approaches in solving this problem, including his use of simple wire-and-paper models. The two quickly seized upon Pauling's notion of a helix, and applied his modeling approach to DNA—despite the criticism from Franklin and Wilkins that models were a less-than-serious approach, unlikely to yield the correct answer. As it would turn out, history might have been written differently had the London group been open to model building.

Watson and Crick were aware that Pauling was now turning his attention to DNA. They were much relieved when, early in 1953, Pauling published his own structure for DNA. It was a triple-helix. They knew immediately that Pauling's model was wrong. They too had devised a similar triple-helix model in late 1951, but were quickly convinced by Rosalind Franklin that their model was incompatible with her x-ray data and thus could not be correct.

The two then moved on to two-chain models, but there were false starts here as well. At first they put the bases facing the outside of the helix. When it became clear from Franklin's data that the bases must be located in the center, Watson next tried to force like-with-like (G-G) hydrogen bonding on the bases. This worked, awkwardly, but only because Watson had been misled by erroneous textbook pictures into using the wrong chemical structure for two of the bases. A colleague in the lab quickly set Watson straight on this point, however.

On a Saturday morning in late February 1953, serendipity and the prepared mind at last came together. Without consciously attempting to find base pairings that satisfied Chargaff's ratios, Watson began moving models of the bases about on his desk. He recounts that "eureka" moment in his engaging 1968 personal account, *The Double Helix*:

Though I initially went back to my like-with-like prejudices, I saw all too well that they led nowhere.... [I] began shifting the bases in and out of other pairing possibilities. Suddenly I became aware that an adenine-thymine pair held in place by two hydrogen bonds was identical in shape to a guanine-cytosine pair held together by at least two hydrogen bonds. All the hydrogen bonds seemed to form naturally; no fudging was required to make the two types of base pairs identical in shape. Some lucky trial-and-error was involved here, but as Crick would later write, "...the important point is that Jim was looking for something significant and immediately recognized the significance of the correct pairs when he hit upon them by chance."

The rest is history. Watson and Crick communicated their DNA model in the April 25, 1953 issue of *Nature*, accompanied by separate papers of Wilkins and Franklin showing how the double helix was consistent with their x-ray data. Watson and Crick's elegantly simple double helix accounts for all of the facts known then and now about DNA's structure. It correctly predicted a mechanism for how the molecule replicates through complementary base pairing, and it made possible the subsequent deciphering of the genetic code. Collaboration, competition, ethical consideration, logic, respect for evidence, skepticism, chance, revision, and accurate prediction—all of these attributes of science are clearly evident in this profound and yet very human chapter in the story of DNA.

*Dr. Stephen M. Pasquale holds a Ph.D. in cellular and integrative biology from Washington University in St. Louis, and an M.S. in pathology and laboratory medicine. He was a postdoctoral fellow in the Department of Pathology & Laboratory Medicine at Washington University School of Medicine. He has been Associate Professor of Biology at Antioch College and at the U.S. Air Force Academy, where he developed and taught courses in developmental biology, genetics, and molecular cell biology.*

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