“Molecular Configuration in Sodium Thymonucleate” (1953), by Rosalind Franklin and Raymond Gosling [1]

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In April 1953, Rosalind Franklin and Raymond Gosling, published "Molecular Configuration in Sodium Thymonucleate," in the scientific journal *Nature*. The article contained Franklin and Gosling´s analysis of their X-ray diffraction pattern of thymonucleate or deoxyribonucleic acid, known as DNA. In the early 1950s, scientists confirmed that genes [6], the heritable factors that control how organisms develop, contained DNA. However, at the time scientists had not determined how DNA functioned or its three-dimensional structure. In their 1953 paper, Franklin and Gosling interpret X-ray diffraction patterns of DNA fibers that they collected, which show the scattering of X-rays from the fibers. The patterns provided information about the three-dimensional structure of the molecule. "Molecular Configuration in Sodium Thymonucleate" shows the progress Franklin and Gosling made toward understanding the three-dimensional structure of DNA.

Scientists worked to understand the three-dimensional structure of DNA since the 1930s. In the early to mid-1900s, scientists tried to determine the structures of many biological molecules, such as proteins, because the structure of those molecules indicated their function. By the 1930s, scientists had found that DNA consisted of a chain of building blocks called nucleotides. The nucleotides contained a ring-shaped structure called a sugar. On one side of the sugar, there is a phosphate group, consisting of phosphorus and oxygen and on the other side of the sugar, another ring-shaped structure called a base. However, scientists had not determined how nucleotides fit together in the overall structure of DNA.

Genetic material, or genes [6], controls how organisms grow, develop, and pass on inheritable traits to offspring. Scientists did not reach the consensus that DNA contained genetic material until the 1950s. In the 1940s and early 1950s, many scientists argued that genes [6] were made of proteins rather than DNA in part because of the published articles about the structures of DNA and proteins. DNA was too simple a molecule to carry genetic information with only four nucleotide bases as opposed to proteins with twenty different amino acids. Oswald Theodore Avery and his colleges at Rockefeller University [7] in New York, New York published experimental evidence that DNA contained the biological factors called genes [6] that dictate how organisms grow and develop. In 1952, Alfred Hershey and Martha Chase, two researchers at the Carnegie Institute of Washington in Cold Spring Harbor, New York, convinced scientists that genes [6] were made of DNA through what was later called the Hershey-Chase experiments. Once scientists agreed that genes [6] were made of DNA, what they learned about DNA´s structure could lead to more knowledge about how genes [6] functioned in DNA.

Even before the Hershey-Chase experiments, Franklin and Gosling had been studying the structure of DNA. The two worked at King´s College London in London, England, under John Turton Randall. Randall hired Franklin in 1951 because she had expertise in a technique he was using to study the structure of molecules called X-ray crystallography. X-ray crystallography involves observing how X-rays scatter from a crystal to determine the arrangement of atoms, or the three-dimensional structure, of that crystal. The scattering of X-rays produces a pattern of dark spots that scientists use to determine the crystal´s structure. During the early 1950s, Franklin and Gosling collected numerous X-ray diffraction patterns of DNA. On 6 May 1952, they collected one of their best patterns, later called Photograph 51, or Photo 51. That diffraction pattern was the one they used for the analysis they present in "Molecular Configuration in Sodium Thymonucleate." Photo 51 shows a series of dark spots radiating from the center of the diffraction pattern in an X shape. Surrounding the X shape is a dark diamond shape, with the darkest parts being at the top and bottom of the diamond.

"Molecular Configuration in Sodium Thymonucleate" is a two-page article with no subsections where Franklin and Gosling deduce structural information about DNA from their X-ray diffraction data. Sodium thymonucleate in the title of the paper refers to DNA extracted from a calf%´s thymus gland, which Franklin and Gosling studied with X-ray crystallography. The article contains only one image, which is Franklin and Gosling´s Photo 51. Franklin and Gosling start the article with a brief discussion of the effect of water content on DNA structure. They follow that discussion with an analysis of the diffraction pattern they present, including mathematical justifications for the structural features of DNA they determined. That analysis includes Franklin and Gosling refuting a structure of DNA that researchers Linus Pauling and Robert Corey proposed the year prior. Franklin and Gosling then summarize their conclusions about the structure of DNA and provide a final paragraph further justifying their claims against the Pauling-Corey model. The authors end the article with acknowledgements and references.

Franklin and Gosling begin "Molecular Configuration in Sodium Thymonucleate" by introducing two structural forms of DNA that they observed and discussed how DNA can transition between those two forms. The authors refer to the structural forms as structure A, the A-form and structure B, the B-form. The two structures of DNA produced different diffraction patterns. Franklin and Gosling explain that an increase or decrease in water content can cause the transition between the two forms. Water content refers to the quantity of water molecules adhered to DNA molecules. The authors describe how changing the humidity of the environment surrounding DNA can change the structure of DNA due to change in water content. They claim that at lower humidity, when fewer water molecules surround DNA, DNA forms the A-form. Conversely, when the humidity is higher, DNA forms the B-form. Photo 51 was an X-ray diffraction pattern of DNA in the B-form.

Franklin and Gosling next introduce their argument that DNA´s structure is helical, or corkscrew-shaped. They include image of Photo 51 at that point in their paper. The authors reference multiple scientists who characterized general features of diffraction patterns when X-ray´s scatter off helical substances. Franklin and Gosling compared their diffraction pattern to the helical structures described by those scientists. They claim that their X-ray data alone, showing some of those general features, cannot prove that DNA is helical.

The authors have other arguments, including one relating to the transition between the A-form and B-form of DNA, that further support their proposal that DNA is helical. According to Franklin and Gosling, when DNA transitions from the B-form to A-form with the loss of water content, the DNA fibers elongate and the spatial arrangement of atoms change. The authors claim, the DNA molecules adopting the B-form, are likely isolated from other DNA molecules because the extra water creates a separation between DNA molecules. The authors reason that the DNA B-form may be able to attain its lowest energy configuration, which is the most stable spatial arrangement of atoms. Franklin and Gosling argue citing a prior study that the most stable arrangement is a helix for a fibrous structure like DNA. In the A-form, where DNA molecules can influence each other, the most stable configuration may not be obtainable. They state that for DNA, the X-ray diffraction pattern of B-form they obtained can provide evidence that justifies the helical structure of DNA.

Once Franklin and Gosling assume that B-form of DNA is helical, they provide a mathematical analysis of their X-ray diffraction pattern of the B-form to further justify that claim. The authors present an equation that describes the structure factor of a single stranded helix. The structure factor describes how an X-ray beam diffracts from a set of atoms in the crystal. In other words, the structure factor equation predicts where dark spots, representing diffracted X-rays, would appear on an X-ray diffraction pattern of a particular molecule. For a helix, the structure factor predicts that the dark spots would align on straight diagonal lines radiating from the center of the pattern creating an X shape, just as in Franklin and Gosling´s diffraction pattern of DNA. Franklin and Gosling account for the presence of the DNA bases in the molecule affect the X-ray diffraction pattern. They assume that the bases are evenly spaced apart. Using their equation and that assumption, Franklin and Gosling account for features they observe in Photo 51. They determine the radius of a DNA fiber and the number of DNA nucleotides per turn of the helix. Franklin and Gosling found the radius to be ten Å, or one millionth of a millimeter. For comparison, the atoms in DNA have radii less than or equal to one Å. Franklin and Gosling also calculate that DNA contains ten nucleotides per turn of the helix.

Using their calculated radius of DNA, Franklin and Gosling describe the arrangement of phosphorus atoms on the opposite side of the sugar from the bases in DNA. They argue that the phosphorus atoms of DNA must be along the outside of the DNA helix. The authors explain that the phosphorus atoms are the most crystallographically important parts of DNA. That may be because the atoms that scatter X-rays the most are the ones with the most electrons, and phosphorus has substantially more electrons than the other atoms found in DNA such as carbon, nitrogen, oxygen and hydrogen. Franklin and Gosling further claim that the most apparent features of their X-ray diffraction pattern are the dark spots that make the X shape that indicate the ten Å radius of the phosphorus atoms. Therefore, the authors state that the phosphorus atoms must be along the outside, or backbone, of the helix.

Franklin and Gosling use their finding that the phosphorus atoms lie on the outside of the DNA helix to challenge the Pauling-Corey model. Pauling and Corey proposed a structure where DNA was made of three separate helical fibers wound around each other, and that in each of those fibers, the phosphorus atoms faced inward, rather than outward as Franklin and Gosling argued. Franklin and Gosling claim that their findings do not support the Pauling-Corey model.

Next in their article, Franklin and Gosling use calculations derived from the A-form of DNA to show that DNA likely contains two strands. Before writing "Molecular Configuration of Sodium Thymonucleate," Franklin and Gosling spent some time researching the A-form of DNA, which included solving the Patterson function, used to solve the phase problem in X-ray crystallography, for that structure. Solving the Patterson function was a way to determine the structure of a molecule directly based on the X-ray data alone, so there was no need to make any outside assumptions or build any models. The process was difficult, but based on the author´s findings related to the A-form, Franklin and Gosling report that the A-form must contain two strands. To carry those findings over to the B-form, Franklin and Gosling go back to the transition between structures A and B. That transition, they claim, is reversible, meaning that DNA can change back and forth between structures A and B as long as the difference in humidity is enough for the transition. Since the change is reversible, the authors argue that it must not involve too much of a change in DNA’s structure, making it unlikely that the number of strands in DNA would change. Therefore, like the A-form, Franklin and Gosling conclude that the B-form contains two strands.

Near the end of "Molecular Configuration in Sodium Thymonucleate" Franklin and Gosling, summarize their findings. They state that DNA is likely helical and that the phosphate atoms must be along the outside of the helix. The authors claim that the diameter of the helix is twenty Å or twice the radius. They also state that DNA probably contains two helical strands. After further justifying that, the phosphorus atoms are along the backbone of DNA, which includes reference to work Franklin and Gosling were in the process of publishing, the authors conclude with acknowledgements to John Turton Randall, James D. Watson, Francis H. C. Crick among others.

Before the publication of “Molecular Configuration in Sodium Thymonucleate”, two scientists at the University of Cambridge in Cambridge, England, James Watson [8] and Francis Crick [9], used many of the data Franklin and Gosling presented in the article to devise their own structure of DNA. In early 1953, Wilkins showed Watson Franklin and Gosling’s most clear diffraction pattern of DNA, likely Photo 51, without Franklin or Gosling´s knowledge. Furthermore, Watson and Crick received a research report Franklin wrote on her experiments. From that information, Watson and Crick developed a structure of DNA that they published in the same issue of Nature that Franklin and Gosling published “Molecular Configuration in Sodium Thymonucleate,” Watson and Crick´s article came directly before Franklin and Gosling’s article in the journal. There is some controversy about the placement of the article in Nature because Franklin was an established researcher the placement should have come first. The Watson-Crick Model of DNA consists of two strands wound together in a double helix. The strands each contain a backbone made up of phosphorus atoms facing outside the helix. Pointing towards the center of the helix are nitrogen-containing units called bases, of which there are four types. Those bases pair with each other in a specific way, meaning that each type of base can bind only to one other type of base. The strands run in opposite directions or anti-parallel to each other, which is as one strand being right side up and the other being upside down. When Wilkins received a draft of Watson and Crick´s proposed DNA model, he insisted that Watson and Crick publish their article alongside Franklin and Gosling´s data.

Franklin and Gosling went on to write two more articles in 1953 about the structure of DNA based on their X-ray crystallography data, including a more detailed description of what happens to DNA when the humidity is increased, and the structural analysis of the A-form of DNA. However, Watson and Crick´s publication garnered most of the attention. In 1962, Watson, Crick, and Wilkins won the Nobel Prize in Physiology or Medicine[10] for their work determining the structure of DNA. Franklin, died in 1958, and therefore not considered for the Nobel Prize. While Franklin and Gosling were not able to draw some conclusions integral to Watson and Crick´s structure of DNA, such as the antiparallel arrangement of the two DNA strands, she and Gosling still independently determined multiple fundamental structural features of DNA. Many historians claim that Franklin´s work, including the findings she and Gosling presented in "Molecular Configuration in Sodium Thymonucleate," has been under-appreciated, though some debate the amount of credit she should receive.

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