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A Structure for Deoxyribose Nucleic Acid

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We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by **Pauling (4)** and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons:

(1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other.

(2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a **radically different structure for the salt of deoxyribose nucleic acid (5)**. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining beta-D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in **the two chains run in opposite directions (6)**. Each chain loosely resembles **Furberg's² model No. 1 (7)**; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's "standard configuration," the sugar being roughly perpendicular to the attached base. There is a residue on each every 3.4 Å. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphorus atom from the fibre axis is 10 Å. As the phosphates are on the outside, cations have easy access to them.



Figure 1
This figure is purely diagrammatic (8). The two ribbons symbolize the two phosphate-sugar

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the



chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-coordinates. One of the pair must be a purine

and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. **These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine) (9).**

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally (10)^{3,4} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data^{5,6} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. **Some of these are given in the following communications (11).** We were **not aware of the details of the results presented there when we devised our structure (12),** which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice (13) that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of coordinates for the atoms, **will be published elsewhere (14).**

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. **We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at King's College, London (15).** One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

¹ Pauling, L., and Corey, R. B., *Nature*, 171, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, 39, 84 (1953).

² Furberg, S., *Acta Chem. Scand.*, 6, 634 (1952).

³ Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, 9, 402 (1952).

⁴ Wyatt, G. R., *J. Gen. Physiol.*, 36, 201 (1952).

⁵ Astbury, W. T., *Symp. Soc. Exp. Biol.* 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).

⁶ Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, 10, 192 (1953).

Annotations

(1) It's no surprise that James D. Watson and Francis H. C. Crick spoke of finding the structure of DNA within minutes of their first meeting at the Cavendish Laboratory in Cambridge, England, in 1951. Watson, a 23-year-old geneticist, and Crick, a 35-year-old former physicist studying protein structure for his doctorate in biophysics, both saw DNA's architecture as the biggest question in biology. Knowing the structure of this molecule would be the key to understanding how genetic information is copied. In turn, this would lead to finding cures for human diseases.

Aware of these profound implications, Watson and Crick were obsessed with the problem—and, perhaps more than any other scientists, they were determined to find the answer first. Their competitive spirit drove them to work quickly, and it undoubtedly helped them succeed in their quest.

Watson and Crick's rapport led them to speedy insights as well. They incessantly discussed the problem, bouncing ideas off one another. This was especially helpful because each one was inspired by different evidence. When the visually sensitive Watson, for example, saw a cross-shaped pattern of spots in an X-ray photograph of DNA, he knew DNA had to be a double helix. From data on the symmetry of DNA crystals, Crick, an expert in crystal structure, saw that DNA's two chains run in opposite directions.

Since the groundbreaking double helix discovery in 1953, Watson has used the same fast, competitive approach to propel a revolution in molecular biology. As a professor at Harvard in the 1950s and 1960s, and as past director and current president of Cold Spring Harbor Laboratory, he tirelessly built intellectual arenas—groups of scientists and laboratories—to apply the knowledge gained from the double helix discovery to protein synthesis, the genetic code, and other fields of biological research. By relentlessly pushing these fields forward, he also advanced the view among biologists that solving major health problems requires research at the most fundamental level of life.

(2) On this date, *Nature* published the paper you are reading.

According to science historian Victor McElheny of the Massachusetts Institute of Technology, the publication of this paper helped change how scientists approached biology. Increasingly in the 1950s, biologists were working out the fundamental mechanisms of life—an undertaking that involved figuring out how genetic information is stored and transmitted. The discovery of the double-helix structure of DNA gave momentum to this kind of work.

Historians wonder how the timing of the DNA race affected its outcome. After years of being diverted by the war effort, scientists were able to focus more on problems such as those affecting human health. Yet, in the United States, many research fields were threatened by a curb on the free exchange of ideas. During the McCarthy era in the early 1950s, the U.S. State Department denied American researcher Linus Pauling a passport to travel internationally. Some think Pauling might have beaten Watson and Crick to the punch if Pauling's ability to travel had not been hampered.

(3) *Nature* (founded in 1869)—and hundreds of other scientific journals—help push science forward by providing a venue for researchers to publish and debate findings. Today, journals also validate the quality of this research through a rigorous evaluation called peer review. Generally at least two scientists, selected by the journal's editors, judge the quality and originality of each paper, recommending whether or not it should be published.

Science publishing was a different game when Watson and Crick submitted this paper to *Nature*. With no

formal review process at most journals, editors usually reached their own decisions on submissions, seeking advice informally only when they were unfamiliar with a subject.

(4) The effort to discover the structure of DNA was a race among several players: world-renowned chemist Linus Pauling at the California Institute of Technology, X-ray crystallographers Maurice Wilkins and Rosalind Franklin at King's College London, and Watson and Crick at the Cavendish Laboratory, Cambridge University.

The competitive juices were flowing well before the DNA sprint was in high gear. In 1951, Pauling narrowly beat scientists at the Cavendish Lab, a top center for probing protein structure, to the discovery that proteins are arranged in structures called alpha-helices. The defeat stung. When Pauling sent a paper to be published in early 1953 that proposed a three-stranded DNA structure, Sir Lawrence Bragg—the head of Cavendish—gave Watson and Crick permission to work full-time on DNA's structure. Cavendish was not about to lose to Pauling twice.

Pauling's proposed three-stranded helix had the bases facing out. While the model was wrong, Watson and Crick were sure Pauling would soon learn his error. They estimated that he was six weeks away from the right answer. Electrified by the urgency—and by the prospect of beating a science superstar—Watson and Crick spent four weeks obsessing about DNA in endless conversations and bouts of model-building to arrive at the correct structure.

In 1952, Wilkins and the head of the King's laboratory denied Pauling's request to view their X-ray photos of DNA—crucial evidence that inspired Watson's vision of the double helix. Pauling had to settle for inferior older photographs. In the same year, he was planning to attend a science meeting in London, where he most likely would have renewed his request in person. But it was the McCarthy era, and the U.S. State Department denied Pauling's request for a passport because of his "un-American" antiwar activism. It was fitting, then, that Pauling, who won the Nobel Prize in Chemistry in 1954, also won the Nobel Peace Prize in 1962, the same year Watson, Crick, and Maurice Wilkins won their Nobel Prize for discovering the double helix.

(5) Here, the young scientists Watson and Crick call their model "radically different" to strongly set it apart from the model proposed by science powerhouse Linus Pauling. This claim was justified. While Pauling's model was a triple helix with the bases sticking out, the Watson-Crick model was a double helix with the bases pointing in and forming pairs of adenine (A) with thymine (T), and cytosine (C) with guanine (G).

(6) This central description of the double-helix model still stands today—a monumental feat considering that the vast majority of research findings are changed over time.

According to science historian Victor McElheny of the Massachusetts Institute of Technology, the staying power of the double-helix theory puts it in a class with Newton's laws of motion. Just as Newtonian physics survived centuries of scientific scrutiny to become the foundation for today's space programs, the double-helix model has provided the bedrock for several research fields since 1953, including the biochemistry of DNA replication, the cracking of the genetic code, genetic engineering, and the sequencing of the human genome.

(7) Norwegian scientist Sven Furberg's DNA model—which correctly put the bases on the inside of a helix—was one of many ideas about DNA that helped Watson and Crick to infer the molecule's structure. To some extent, they were synthesizers of these ideas. Doing little laboratory work, they gathered clues and advice from other experts to find the answer. Watson and Crick's extraordinary scientific preparation, passion, and collaboration made them uniquely capable of this synthesis.

(8) A visual representation of Watson and Crick's model was crucial to show how the components of DNA fit together in a double helix. In 1953, Crick's wife, Odile, drew the diagram used to represent DNA in this paper. Scientists use many different kinds of visual representations of DNA.

(9) The last hurdle for Watson and Crick was to figure out how to arrange DNA's four bases (adenine,

thymine, guanine, and cytosine) inside the double helix without distorting the molecule. To visualize the answer, Watson built cardboard cutouts of the bases. Early one morning, as Watson moved the cutouts around on a tabletop, he found that the overall shape of an adenine molecule paired with a thymine molecule was similar to the overall shape of a guanine-cytosine pair. He immediately realized that arranging the bases in these pairs made a DNA structure without bulges or strains. Watson solved the puzzle "not by logic but serendipity," Crick recalled in his book *What Mad Pursuit*.

Watson and Crick picked up this model-building approach from eminent chemist Linus Pauling, who had successfully used it to discover that some proteins have a helical structure.

(10) This sentence refers to the work of Erwin Chargaff, a biochemist at Columbia University. In the late 1940s, Chargaff analyzed the proportions of the four different types of base molecules in DNA, and found that DNA always contains equal amounts of guanine and cytosine, and equal amounts of adenine and thymine.

The significance of this discovery remained unclear until February 1953. That's when Watson figured out how DNA's four bases paired with one another. By fiddling with cardboard cutout versions of the base molecules, he discovered that adenine always pairs with thymine, and guanine always pairs with cytosine. Now Chargaff's finding made perfect sense to Watson and Crick: If every adenine and thymine are paired in DNA, there must be an equal number of these two molecules. The same goes for guanine and cytosine.

(11) Alongside the Watson-Crick paper in the April 25, 1953, issue of *Nature* were separately published papers by scientists Maurice Wilkins and Rosalind Franklin of King's College, who worked independently of each other. The Wilkins and Franklin papers described the X-ray crystallography evidence that helped Watson and Crick devise their structure. The authors of the three papers, their lab chiefs, and the editors of *Nature* agreed that all three would be published in the same issue.

The "following communications" that our authors are referring to are the papers by Franklin and Wilkins, published on the journal pages immediately after Watson and Crick's paper. They (and other papers) can be downloaded as PDF files ([Adobe Acrobat](#) required) from [Nature's 50 Years of DNA](#) Web site.

Here are the direct links:

Molecular Configuration in Sodium Thymonucleate

Franklin, R., and Gosling, R. G.

Nature 171, 740-741 (1953)

<http://www.nature.com/nature/dna50/franklingosling.pdf>

Molecular Structure of Deoxypentose Nucleic Acids

Wilkins, M. H. F., Stokes, A. R., & Wilson, H. R.

Nature 171, 738-740 (1953)

<http://www.nature.com/nature/dna50/wilkins.pdf>

(12) Here, Watson and Crick say that they "were not aware of the details" of the work of King's College scientist Rosalind Franklin—a statement that marks what many consider an inexcusable failure to give Franklin proper credit.

According to Lynne Elkin, a science historian at California State University, Hayward, it's true that Watson and Crick were not aware of all the details of Franklin's work, but they were aware of enough of the details to discover the structure of DNA. Yet this paper does not ever formally acknowledge her, instead concealing her significant role by saying they "were not aware" of her work.

What exactly was Franklin's research, and how did Watson and Crick gain access to it? While they were busy building their models, Franklin was at work on the DNA puzzle using X-ray crystallography, which

involved taking X-ray photographs of DNA samples to infer their structure. By late February 1953, her analysis of these photos brought her close to the correct DNA model.

But Franklin stopped her work on DNA because she was frustrated with a strained environment at King's, one that pitted her against her colleagues. In an institutional culture that barred women from the dining room and other social venues, she was denied access to the informal discourse that is essential to any scientist's work. Seeing no chance for a tolerable professional life at King's, Franklin decided to take another job. As she was preparing to leave, she turned her X-ray photographs over to her colleague Maurice Wilkins.

Then, in perhaps the most pivotal moment in the search for DNA's structure, Wilkins, a longtime friend of Crick, showed Watson one of Franklin's photographs without Franklin's permission. Watson recalled, "The instant I saw the picture my mouth fell open and my pulse began to race." To Watson, the cross-shaped pattern of spots in the photo meant that DNA had to have a helical structure. Franklin's photograph was critical in solving the problem, as Watson admitted in his 1968 book, *The Double Helix*.

Watson and Crick also had access to an internal report from the Medical Research Council, a British agency for funding life sciences, summarizing much of Franklin's unpublished work on DNA, including precise measurements of the molecule. As the Cavendish representative to the agency, scientist Max Perutz had a copy of the report, and when Crick asked to see it, Perutz obliged. While the report was not confidential, science historian Lynne Elkin contends that "showing unpublished work to an unacknowledged competitor was a questionable act which justifiably infuriated" John Randall, the head of King's.

Crick later said the data in the report enabled him to reach the significant conclusion that DNA has two chains running in opposite directions. Although Franklin was listed in the acknowledgements section with other scientists, there was no specific mention of her contributions.

Was it unethical for Wilkins to reveal the photographs, or for Perutz to hand over the King's report? How should Watson and Crick have recognized Franklin for her contribution to their paper? For decades, scientists and historians have wrestled over these issues.

To read more about Rosalind Franklin and her history with Wilkins, Watson, and Crick, see the following Web sites:

"Light on a Dark Lady" by Anne Piper, a lifelong friend of Franklin's

<http://www.physics.ucla.edu/~cwp/articles/franklin/piper.html>

"The Double Helix and the Wronged Heroine," an essay on *Nature's* "Double Helix: 50 years of DNA" Web site

http://www.nature.com/cgi-taf/DynaPage.taf?file=/nature/journal/v421/n6921/full/nature01399_fs.html

A review of Brenda Maddox's recent book, *Rosalind Franklin: The Dark Lady of DNA*, in *The Guardian* (UK)

<http://books.guardian.co.uk/whitbread2002/story/0,12605,842764,00.html>

(13) This phrase and the sentence it begins may be one of the biggest understatements in biology. Watson and Crick realized at the time that their work had important scientific implications beyond a "pretty structure." In this statement, the authors are saying that the base pairing in DNA (adenine links to thymine and guanine to cytosine) provides the mechanism by which genetic information carried in the double helix can be precisely copied. Knowledge of this copying mechanism started a scientific revolution that would lead to, among other advances in molecular biology, the ability to manipulate DNA for genetic

engineering and medical research, and to decode the human genome, along with those of the mouse, yeast, fruit fly, and other research organisms.

(14) This paper is short because it was intended only to announce Watson and Crick's discovery, and because they were in a competitive situation. In January 1954, they published the "full details" of their work in *Proceedings of the Royal Society*. This "expound later" approach was common in science in the 1950s. In fact, Rosalind Franklin did the same thing, supplementing her short April 25 paper with two longer articles.

Journals today offer scientists a greater variety of publishing formats than journals in the 1950s. *Nature* now has more than five different options, most of which are subjected to a rigorous evaluation known as peer review. Since Watson and Crick largely presented a hypothesis instead of new data in this paper, *Nature* would likely have published it today as an "Analysis" paper—one of the journal's shorter peer-reviewed formats. This paper was not peer-reviewed—*Nature* had no formal review process in the 1950s—but it would have been peer-reviewed if submitted today.

For many decades, conferences have also been an important forum for researchers to present their work. Watson reported his and Crick's results at the prestigious annual symposium at Cold Spring Harbor Laboratory in June 1953. Meetings continue to be a significant part of the culture of science at Cold Spring Harbor.

(15) Science historian Lynne Elkin calls this sentence an understatement. She argues that Watson and Crick were "more than stimulated" by Franklin's work—and had "more than a general knowledge" of it—because they relied on her X-ray photograph and her specific DNA measurements.

Interestingly, this sentence contained a stronger acknowledgment of Franklin's work in an early draft of the paper: "We have also been stimulated by the very beautiful experimental work of Dr. M. H. Wilkins and his co-workers at Kings College, London." Elkin suggests that the phrase "very beautiful" is most likely a nod to Franklin's X-ray photograph. The same draft also acknowledged Franklin's work with the sentence: "It is known that there is much unpublished experimental material." When Maurice Wilkins read the draft, he advised Watson and Crick to delete this sentence and the phrase "very beautiful." They agreed to his suggestion.

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