Who said 'helix'?

Right and wrong in the story of how the structure of DNA was discovered.

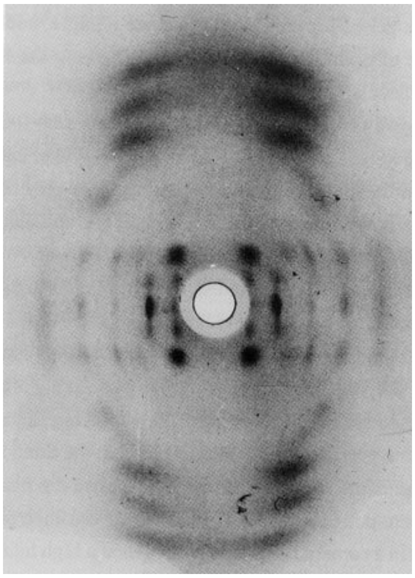
Watson Fuller

The celebrated model of DNA, put forward in this journal in 1953 by James Watson and Francis Crick, is compellingly simple, both in its form and its functional implications (see www.nature.com/nature/dna50). At a stroke it resolved the puzzle inherent in the X-ray diffraction photograph (see right) shown by Maurice Wilkins at a scientific meeting in Naples in the spring of 1951. This was the pattern that so excited Jim Watson, who, in *The Double Helix*[1], wrote: "Maurice's X-ray diffraction pattern of DNA was to the point. It was flicked on the screen near the end of his talk. Maurice's dry English form did not permit enthusiasm as he stated that the picture showed much more detail than previous pictures and could, in fact, be considered as arising from a crystalline substance. And when the structure of DNA was known, we might be in a better position to understand how genes work."

DNA structure investigations

This pattern had been recorded at King's College London by Raymond Gosling from a bundle of thin fibres drawn by Wilkins from DNA provided by Rudolf Signer in early 1950. Alec Stokes, also at King's, pointed out that apart from strong 3–4-Å features at the top and bottom of the pattern, there was no diffraction close to the meridian, indicating that DNA had a helical structure[2]. From measurements by Gosling, the vertical separation of the rows of spots (layer lines) could be identified with a helix pitch of 28 Å, and the lateral spacing of spots with helices packed together like 20-Å diameter cylinders. The strong 3–4-Å features had previously been observed in Bill Astbury's laboratory in Leeds and had been attributed to diffraction from planar bases in DNA, stacked like "a pile of plates"[3].

Despite the relatively primitive X-ray equipment of the time, by the end of 1950 the group at King's had not only demonstrated that DNA has a highly regular structure, but had extracted from the diffraction data important clues about the shape of the molecule and the dimensions of features in it. Wilkins and his colleagues had good cause for optimism, and it was expected that the arrival of Rosalind Franklin from a Paris laboratory, where she had already successfully exploited X-ray diffraction techniques, would further strengthen the group. Much has been written about the clashes, particularly with Wilkins, that marked Franklin's two years at King's (see, for example, refs 4, 5). Here I aim to provide a more accurate



COURTESY R. G. GOSLING & M. H. F. WILKINS

A crystalline X-ray diffraction pattern of DNA, taken in June 1950 by Raymond Gosling, from a multifibre specimen made by Maurice Wilkins from DNA supplied by Rudolf Signer. A Raymax X-ray tube was used with a Unicam camera, filled with hydrogen (90% relative humidity). In Wilkins' words: "now it was really obvious — genes had a crystalline structure".

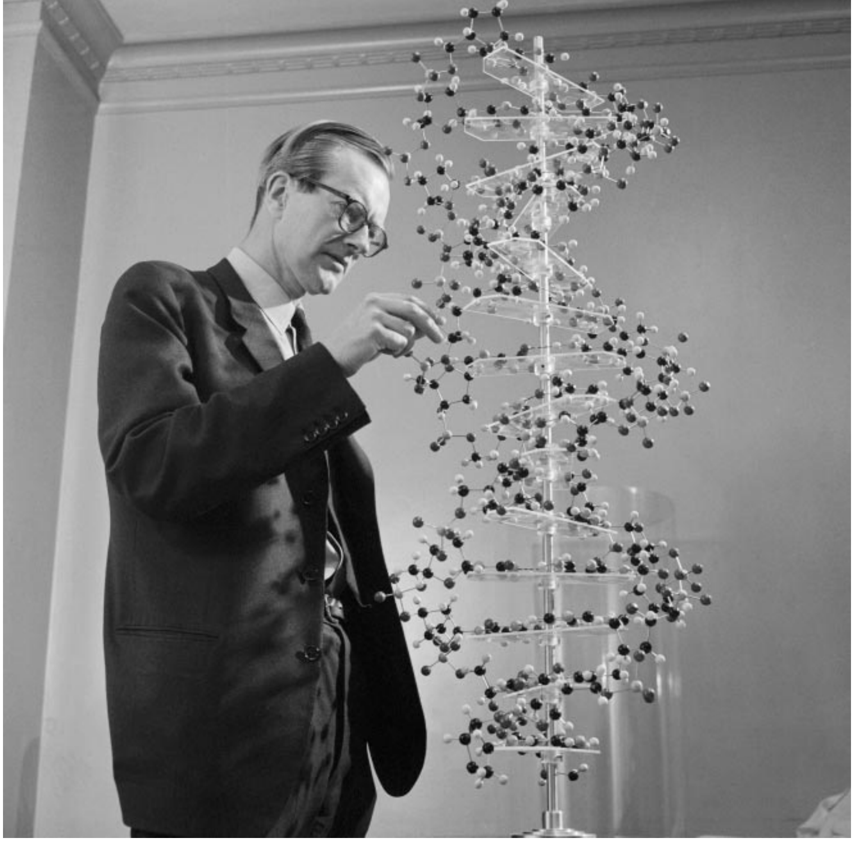
perspective on the scientific role of Wilkins than is often apparent in popular narratives of the discovery — and even among some sections of the scientific community.

Certainly Franklin, an established researcher, had good reason to feel that she had been misled by a letter from the head of the King's laboratory, John Randall, about the degree of independence she could expect in her X-ray diffraction studies of DNA. Equally, Wilkins could feel outraged at being abruptly excluded — with no prior notice — from the very aspect of the DNA work on which he and Gosling had made such excellent progress. Randall, with his experience of directing an industrial research laboratory and of sharply focused, technological war-directed research, might have felt that the *laissez-faire* ethos of university research ought to be superseded. Moving staff around like pieces on a chess board could expedite the results that would justify generous levels of public funding. But almost a year before the end of her three-year fellowship, Franklin, to widespread relief at King's, left to join J. D. Bernal's research group in Birkbeck College. As a result, Randall must have seriously questioned his own actions and have wondered whether, but for the conflicts engendered by the letter he had written to her in Paris, the double-helical structure of DNA might not have been discovered in London rather than in Cambridge. In fairness to Randall, it was his energy, enterprise and vision in establishing the King's laboratory that allowed the experimental work that stimulated the discovery to take place.

The proposed double-helical model for DNA is commonly described as the most significant discovery of the second half of the twentieth century. Inevitably, the contributions of the principal protagonists have been subjected to minute scrutiny. Crick, Franklin, Watson and Wilkins have all endured hostile criticism and snide disparagement of their roles in the story. Franklin has loyal, influential and persistent champions, and in particular has had her reputation boosted, mainly at Wilkins' expense. Some have gone so far as to ask whether, if Franklin, who died at the age of 37 in 1958, had lived, she would have shared the Nobel prize for the discovery of the structure of DNA. As the prize is never shared by more than three people, the implication is that Wilkins would have been excluded.

Humidity-driven transitions

By far the most significant contribution by Franklin while at King's was the exploitation of the fine-focus X-ray generator developed by Werner Ehrenberg and Walter Spear at Birkbeck College, London, previously obtained by Wilkins, and a commercial X-ray microcamera in experiments in which the humidity of the specimen environment was accurately controlled. Although in their earlier experiments Wilkins and Gosling had realized serendipitously that DNA should be studied in a moist environment (famously maintained by stretching a condom around the camera collimator), they had not achieved precise control nor been able to sustain very high humidities reproducibly. Franklin's improvements allowed her and Gosling to undertake a systematic study of the manner in which the X-ray diffraction from DNA changed with the water content of the fibre and to obtain patterns with much sharper diffraction maxima[6]. They identified two forms, 'A' (a low-humidity form) and 'B' (high humidity), together with intermediate patterns of A mixed with B. Both forms had been observed by previous workers, notably the image shown above (the A form) recorded by Wilkins and co-workers, as well as less-good B-form patterns by them and in Astbury's laboratory[7]. The analysis of the improved A and B patterns by Franklin and Gosling had important consequences, positive and negative,



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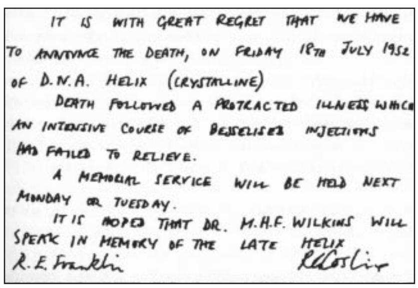
Maurice Wilkins in 1962 posing for reporters following the announcement that he, Watson and Crick had won the Nobel prize for their work on the elucidation of the structure of DNA.

both for the work at King's and for the development of the double-helical model.

A typical crystal or fibre studied by X-ray diffraction contains billions of molecules; the general assumption is that the purer the sample and the greater the degree of regularity with which the molecules are arranged, the sharper will be the spots in its diffraction pattern. The position of the spots reflects the disposition of the molecules in the crystal or fibre, and the overall intensity variation across the pattern, which can be imagined as being 'sampled' at the points at which the spots appear, is determined by the overall shape of the molecule. Determination of the arrangement of the molecules from the position of the diffraction spots was relatively straightforward, but determination of the shape of the individual molecule from the relative intensities of these spots required a combination of insight, experience and good fortune.

Franklin and Gosling concentrated their efforts on analysis of the A pattern which, because it had sharp spots across its whole extent, was designated as crystalline, rather than on the B pattern, which was designated semi-crystalline because all of the sharp spots were confined to the centre with continuous streaks in the outer regions. Although they pursued their goal with high analytical skill, methodological innovation and a willingness to undertake arduous calculations, the endeavour was unsuccessful. Franklin had been adamant that the investigation should proceed by a detailed analysis of the X-ray data rather than a more intuitive



IT IS WITH GREAT REGRET THAT WE HAVE
TO ANNOUNCE THE DEATH, ON FRIDAY 18TH JULY 1952
OF D.N.A. HELIX (CRYSTALLINE)
DEATH FOLLOWED A PROTRACTED ILLNESS WHICH
AN INTENSIVE COURSE OF BESSELISED INJECTIONS
HAD FAILED TO RELIEVE.
A MEMORIAL SERVICE WILL BE HELD NEXT
MONDAY OR TUESDAY.
IT IS HOPED THAT DR. M.H.F. WILKINS WILL
SPEAK IN MEMORY OF THE LATE HELIX
R.E. Franklin

***In Memoriam* card sent by Rosalind Franklin and Raymond Gosling to Maurice Wilkins in July 1952 (published in ref. 4). The "INTENSIVE COURSE OF BESSELISED INJECTIONS" refers to the expression derived by Alec Stokes for diffraction from helical molecules in terms of cylindrical Bessel functions.**

approach, building on Stokes' inference that the overall distribution of diffracted intensity in both the A and B patterns, in particular the lack of intensity along the meridian, strongly suggested that the structure of DNA in both forms was helical. Opinions at King's became increasingly polarized, with Franklin more and more strongly identified with an anti-helical view, expressed most triumphantly in the *In Memoriam* card distributed by Franklin and Gosling in July 1952 announcing that their analysis of the A form heralded the death of the helix (see above). However, Aaron Klug, from his access to Franklin's notebooks and draft papers, has shown that Franklin was not as anti-helical as was widely believed in the months leading up to the discovery of the double helix, and that indeed she was working on the assumption that the B form at least was helical[8,9].

In the much improved B-type pattern obtained by Franklin and Gosling in May 1952, the helical features are very clear. It was this pattern that Gosling passed to Wilkins without any caveat regarding its use. Wilkins, perhaps naively, but totally in character given his strong commitment to sharing scientific information, showed it to Watson on his crucial visit to King's at the end of January 1953. Watson immediately recognized this as the clearest evidence yet for a helical structure. Accounts vary as to the details of the B pattern Watson took back to Cambridge. Some have read signs of unease into the Watson and Crick paper of 1953, in that it seems evasive about the extent to which they used information from the King's laboratory to define their model, in particular, the helix pitch of 34 Å with 10 residues per turn and the strongly scattering phosphate groups at a radius of 10 Å.

Watson and Crick, as Watson notoriously stated in *The Double Helix*, also had the benefit of seeing a report that was submitted by King's scientists to the Medical Research Council (MRC). This was given to Max Perutz in the Cambridge laboratory in his role as a member of a review committee. Views differ over the degree of confidentiality of this document and whether Perutz behaved properly in showing it to his colleagues, including Crick. In Perutz's defence, the point has been made that one of the purposes of these reports was to make the various MRC laboratories aware of what the others were doing. Recollections differ on how much of the information in this report (written in early September 1952 for a committee visit in December 1952, and shown to Crick in February 1953) was included in a seminar by Franklin at King's in November 1951 (to which Crick was invited but sent Watson). This report included the determination by Franklin and Gosling of the symmetry of the unit cell of the A form. This was to prove, in the hands of Crick, crucial information, as it implied that DNA had two-fold symmetry about an axis perpendicular to the helix axis, and therefore, if it was a two-stranded structure, that the direction of one chain should be opposite to that of the other.

Whether because of discomfort over the less than customary channels for the flow of information from King's to Cambridge or not, the double-helical model is presented in the epoch-making paper by Watson and Crick more as a revelation to prepared minds than the product of a series of logical steps from crucial experimental data. Thus Watson and Crick were at pains to stress in their paper the importance of further X-ray work to confirm their hypothesis. Over the next decade, Wilkins and his co-workers indeed obtained X-ray diffraction patterns that were much better defined, and developed new techniques for their analysis[10–12].

Two papers, one by Wilkins, Stokes and Herbert Wilson, the other by Franklin and Gosling, were published alongside that of Watson and Crick (see www.nature.com/nature/dna50), showing that the Watson and Crick model was consistent with their X-ray diffraction patterns. The paper by Wilkins *et al.* also referred to A- and B-type diffraction patterns from various sources and notes the "most marked" correspondence between their presentation of the diffraction expected from the double-helical model and "the exceptional photograph obtained by our colleagues, R. E. Franklin and R. G. Gosling". For their part, Franklin and Gosling noted that Stokes and Wilkins were the first to propose helical structures as a result of direct studies of nucleic-acid fibres. Indeed, in a letter to Crick in early 1952, Wilkins had already sketched out the diffraction pattern from oriented sperm heads showing B-type diffraction, with the cross-like intensity distribution characteristic of a helix on layer lines in the centre of the pattern and meridional diffraction at the top and bottom (see above right).

Molecular model building

Crucial for the success of Watson and Crick's approach had been the use of molecular models based on knowledge of chemical bonding determined from stereochemistry and X-ray single-crystal studies of molecular components. The models allowed rotation about single bonds in the chemical structure, so that by systematically varying these orientations the various sterically permissible conformations that were also compatible with the biological, chemical and physical data on the molecule could be identified.

Franklin's insistence on direct analysis of the X-ray data from the fully crystalline A-form and her dismissal of model building, so successful in the discovery of the α-helix, were serious errors of judgement. Crick especially had a strong commitment to model building. It is important to emphasize, in view of the attention that has been given to the exploitation of King's data by the Cambridge workers, that before the discovery of the double helix, Crick encouraged Wilkins and Franklin to build models and provided them with jigs developed in Cambridge for constructing the atomic components.

A particular advantage of molecular models is that they provide a framework within which information from a whole range of physical, chemical and biological techniques can be correlated and integrated. The unfortunate consequences of Franklin's approach in insisting on single-crystal techniques in the analysis of the A form was that she isolated herself from other workers and the information that they could provide. Although Wilkins' trips to Cambridge may well have resulted in a rather one-sided flow of information, they were made in the spirit of the multi-

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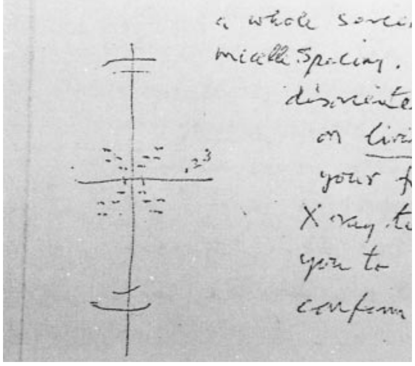

Part of a letter from Maurice Wilkins to Francis Crick (early 1952) showing a sketch of B-type diffraction from oriented sperm heads. The numbers 1, 2 and 3 identify the first three layer lines. The cross-like distribution of intensity on these layer lines is characteristic of diffraction from a helical structure. On the basis of the angle of the cross, Wilkins estimated the angle of ascent of the helix to be about 40°. Meridional diffraction on higher-order layer lines at the top and bottom of the pattern is also indicated.

disciplinary approach needed for the structure determination of a biological macromolecule such as DNA. The Fourier transform approach to X-ray data analysis from fibres, as suggested by Stokes, also has the advantage over single-crystal methods in that it can reveal at an early stage general features of the molecular structure. It showed in the case of DNA that the molecule is helical, and it yielded parameters defining the helix geometry.

Openness

The history of the discovery of DNA is too often presented in popular accounts in terms of results 'stolen' by Watson and Crick, with Franklin as the victim. Yet in the complex interactions in and between the two laboratories, it is not sustainable to view Franklin merely as a victim of other people's actions. When she joined King's she was given the superior material procured by Wilkins from Signer, which had consistently given much better diffraction patterns than any samples from other sources. In Gosling she was given a research student who had worked with Wilkins and was already experienced in X-ray data collection and analysis. In Stokes she had access to outstanding expertise in diffraction theory and in Wilkins she had the opportunity to collaborate with someone who already had an international reputation for physical studies on DNA.

KING'S COLLEGE LONDON

King's reunited: (from left) Raymond Gosling, Herbert Wilson, Maurice Wilkins and Alec Stokes at a celebration for DNA's 40th anniversary.

It was to the sad detriment not only of herself but also of the King's laboratory as a whole that Franklin chose to work in isolation on a problem, the solution of which depended on confluent results from several workers using different techniques. This is particularly a matter for regret because the experimental work that Franklin performed at King's was of the highest quality; her use of Patterson techniques to obtain structural information from fibre-diffraction data was highly innovative, if disappointing in its outcome. Franklin's approach contrasted markedly with that of Wilkins, who made his results freely known. It is appropriate therefore to end this account with an expression of Wilkins' attitude to science as reflected in his letter to Crick (quoted in ref. 7) after he had visited Cambridge to see the Watson and Crick model.

> Dear Francis
> I think you're a couple of old rogues but you may well have something. I like the idea. Thanks for the MSS. I was a bit peeved because I was convinced that the 1:1 ratio was significant and had a 4 planar group sketched and was going to look into it and as I was back again on helical schemes I might, given a little time, have got it. But there is *no good grousing* — I think it's a very exciting notion and who the hell got it isn't what matters.

It may well be that historians of science will choose to view this affirmation as a mere epitome of the stiff upper lip. But we must hope that it will be seen for what it is — a principled expression of an attitude, now all too rare, that both the scientific and the wider community should applaud. ■

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