

DNA Helix

I recently came across Dr. E. Chargaff's review (1) of J. D. Watson's book *The Double Helix* (2). I was disturbed by his quotation of an episode which relates how I handed to Watson and Crick an allegedly confidential report by Professor J. T. Randall with vital information about the x-ray diffraction pattern of DNA.

As this might indicate a breach of faith on my part, I have tried to discover what historical accuracy there is in Watson's version of the story, which reads as follows (3):

Even during good films I found it almost impossible to forget the bases. The fact that we had at last produced a stereochemically reasonable configuration for the backbone was always at the back of my head. Moreover, there was no longer any fear that it would be incompatible with the experimental data. By then it had been checked out with Rosy's precise measurements. Rosy, of course, did not directly give her data. For that matter, no one at King's realized they were in our hands. We came upon them because of Max's membership on a committee appointed by the Medical Research Council to look into the research activities of Randall's lab. Since Randall wished to convince the outside committee that he had a productive research group, he had instructed his people to draw up a comprehensive summary of their accomplishments. In due time this was prepared in mimeographed form and sent routinely to all committee members. As soon as Max saw the sections by Rosy and Maurice, he brought the report in to Francis and me. Quickly scanning its contents Francis sensed with relief that following my return from King's I had correctly reported to him the essential features of the "B" pattern. Thus only minor modifications were necessary in our backbone configuration.

Watson showed me his book twice in manuscript; I regret that I failed to notice how this passage would be interpreted by others and did not ask him to alter it. The incident, as told by Watson, does an injustice to the history of one of the greatest discoveries of the century. It pictures Wilkins and Miss Franklin jealously trying to keep their data secret, and Watson and Crick getting hold of them in an underhand way, through a confidential report passed on by me. What historical evidence I have been able to collect does not corroborate this story. In summary, the committee of which I was a member did not exist to "look into the research activities of Randall's lab," but to bring the different Medical Research Council units working in the field of biophysics into touch with each other. The report

was not confidential and contained no data that Watson had not already heard about from Miss Franklin and Wilkins themselves. It did contain one important piece of crystallographic information useful to Crick; however, Crick might have had this more than a year earlier if Watson had taken notes at a seminar given by Miss Franklin.

I discarded the papers of the committee many years ago but the Medical Research Council kindly found them for me in their archives. According to their records there were, in fact, two committees. First, the Biophysics Research Unit Advisory Committee, set up at the beginning of 1947 "to advise regarding the scheme of research in biophysics under the direction of Professor J. T. Randall." Neither Randall nor I were members of that committee; I did not know of its existence until recently. It held its final meeting in October 1947, 5 years before the episode related by Watson. Later that year the Council set up the Biophysics Committee "to advise and assist the Council in promoting research work over the whole field of biophysics in relation to medicine." This new committee consisted mainly of the heads of all the Medical Research Council units related to biophysics, and included Randall and myself. We visited each laboratory in turn; the director would tell the others about the research in his unit and circulate a report. The reports were not confidential. The committee served to exchange information but was not a review body; we were never asked for an opinion of the work we saw. The Medical Research Council dissolved it in 1954, in the words of the official letter because "the Committee has fulfilled the purpose for which it was set up, namely to establish contact between the groups of people working for the Council in this field" (Appendix 1).

On 15 December 1952, we met in Randall's laboratory where he gave us a talk and also circulated the report referred to in Watson's book. As far as I can remember, Crick heard about its existence from Wilkins, with whom he had frequent contact, and either he or Watson asked me if they could see it. I realized later that, as a matter of courtesy, I should have asked Randall for permission to show it to Watson and Crick, but in 1953 I was inexperienced and casual in administrative matters and, since the report was not confidential, I saw no reason for withholding it.

I now come to the technical details of the report. It includes one short section describing Wilkins' work on DNA and nucleoprotein structures and then another on "X-ray studies of calf thymus DNA" by R. E. Franklin and R. G. Gosling. They are reproduced in Appendix 2 below. Note that they contain only two pieces of numerical data. One is the length of the fiber axis repeat of 34 Å in the wet or "B" form of DNA; this is the biologically more important form, solved by Watson and Crick. The other piece consists of the unit-cell dimensions and symmetry of the partially dried "A" form, which was the one discovered and worked on by Wilkins and Miss Franklin, to be solved later by Wilkins and his colleagues. The report contained no copies of the x-ray diffraction photographs of either form.

We can now ask if this section really contained "Rosy's precise measurements needed to check out" Watson and Crick's tentative model and whether it is true that "Rosy did not give us her data . . . and no one at King's realized that they were in our hands." In fact, the report contained no details of the vital "B" pattern apart from the 34 Å repeat, but Watson, according to his own account heard them from Wilkins himself, shortly before he saw the report. This story is told in chapter 23, relating Watson's visit to King's College in late January 1953 where Miss Franklin supposedly tried to hit him and where Wilkins showed him a print of one of her exciting new x-ray photographs of the "B" form of DNA. The next chapter (24) begins as follows: "Bragg was in Max's office when I rushed in the next day to blurt out what I had learned. Francis was not yet in, for it was a Saturday morning and he was home in bed glancing at the *Nature* that had come in the morning mail. Quickly I started to run through the details of the "B" form of DNA, making a rough sketch to show the evidence that DNA was a helix which repeated its pattern every 34 Å along the helical axis." The incident of the report comes in the following chapter (25) and is dated early 1953.

It is interesting that a drawing of the "B" patterns from squid sperm is also contained in a letter from Wilkins to Crick written before Christmas 1952. All this clearly shows that Wilkins disclosed many, even though perhaps not all, of the data obtained at King's to either Watson or Crick.

Turning now to the x-ray pattern of the "A" form, this had been the subject of a seminar given by Miss Franklin at King's in November 1951, an occasion described by Watson in chapter 10. After Miss Franklin's tragic death in 1958, her colleague, Dr. A. Klug, preserved her scientific papers; among these are her notes for that seminar, which he now kindly showed me. These notes include the unit-cell dimensions and symmetry of the "A" form which were circulated in the report a year later.

Watson, according to his own account, had failed to take notes at Miss Franklin's seminar, so that he could not give the unit-cell dimensions and symmetry to Crick afterward. Crick tells me now that the report did bring the monoclinic symmetry of the unit cell home to him for the first time. This really was an important clue as it suggested the existence of twofold symmetry axes running normal to the fiber axis, requiring the two chains of a double helical model to run in opposite directions, but he could clearly have had this clue much earlier.

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References and Notes

1. E. Chargaff, *Science* **159**, 1448 (1968).
2. J. D. Watson, *The Double Helix, A Personal Account of the Discovery of the Structure of DNA* (Atheneum, New York, 1968).
3. —, *ibid.*, p. 181.
4. I thank the Medical Research Council, Dr. A. Klug, and Dr. R. Olby for supplying me with historical documents, and Sir J. Randall, Professor M. H. F. Wilkins, and Dr. R. G. Gosling for permission to publish their report.

10 April 1969

Appendix 1

27 April 1954

Dear Perutz

The Council have been considering the future of their Biophysics Committee, which was appointed in 1947 and would be due for reconstitution if it were to be kept in being. After consultation with the Chairman and others, they have come to the conclusion that *the Committee has fulfilled the purpose for which it was set up, namely to establish contact between the different groups of people working for the Council in this field*. It has accordingly been decided that the Committee should now be discharged. I am asked by the Council to send you their best thanks for all the help that you have given to their work by serving on this Committee.

Yours sincerely,
Landsborough Thomson
(Secretary to the Biophysics Committee)

Appendix 2

Report by Professor J. T. Randall
to the Medical Research Council,
dated December 1952

Nucleic Acid Research

The research on nucleic acids, like that on collagen, has both a structural and a biological interest. Some time ago Wilkins found that fibres from sodium desoxyribonucleate gave remarkably good x-ray fibre diagrams. He also examined the optical properties of the fibres in relation to their molecular structure. The detailed examination of the structure has been continued by Miss Franklin and R. G. Gosling, and Wilkins has concentrated on a study of the oriented nucleoprotein of sperm heads. The biological implications of this work are indicated later in this section.

The study of nucleic acids in living cells has been continued by Walker (tissue cultures) and by Chayen (plant root meristem cells); and lately Wilkins and Davies have been measuring the dry weight of material in *Tradescantia* pollen grains during the course of cell division by means of interference microscopy. Thus, while the work of Walker on nucleic acid content of nuclei relates only to part of the cell contents, the interference microscope enables the total content of the cell, other than water, to be measured.

Desoxyribose Nucleic Acid and Nucleoprotein Structure (M. H. F. Wilkins)

A molecular structure approach has been made to the question of the function of nucleic acid in cells.

First, x-ray evidence shows that DNA from all kinds of sources has the same basic molecular configuration which is little (if at all) dependent on the nucleotide ratio. Some grouping of polynucleotide chains takes place to give ~20 Å diameter rod-shaped units, and the internal chemical binding which holds each unit together is not affected much by the normal extraction procedure. The basic point is to find the general nature of this structure and the hydrogen bonding etc. in it. Using two dimensional data, the most reasonable interpretation was in terms of a helical structure and the experimental evidence for such helices was much clearer than that obtained for any protein. The crystalline material gives an x-ray picture with considerable elements of simplicity which could be accounted for by the helical ideas, but three dimensional data show apparently that the basic physical explanation of the simplicity of the picture lies in some quite different and, a priori, much less likely structural characteristic. The 20 Å units, while roughly round in cross-section, appear to have highly asymmetric internal structure.

The same general configuration appears to exist in intact sperm heads and synthetic or extracted nucleoprotein, and in bacteriophage (and not in insect virus

where the protein is different). It appears that the protein is probably bound electrostatically on the outside of the nucleic acid units and does not alter their structure. In some sperm the whole head has a crystalline (but somewhat imperfect) structure. In these sperm, the protein has very low molecular weight and it will be especially interesting to find if any high molecular weight protein exists in such sperm heads. If not, all the genetical characteristics may be supposed to lie in the DNA (as in bacteriophage). Biochemical study of the composition of the protein is planned. In other kinds of cell nucleus with different biological function the proteins are quite different. The main idea is to find the structure of the DNA first, then how it is linked to protein in the crystalline sperm heads, and then attempt to elucidate the more complex structure of the other kinds of cell nuclei. It may be that the characteristic x-ray picture of DNA is especially related to a particular function of the nuclear nucleoprotein. In this way molecular structure and cytochemical studies begin to overlap.

X-ray Studies of Calf Thymus DNA (R. E. Franklin and R. G. Gosling)

(a) *The Role of Water*: The crystalline form of calf thymus DNA is obtained at about 75 percent RH and contains about 20 percent by weight of water.

Increasing the water content leads to the formation of a different structural modification which is less highly ordered. The water content of this form is ill-defined.

The change from the first to the second structure is accompanied by a change in the fibre-axis repeat period of 28 Å to 34 Å and a corresponding microscopic length-change of the fibre of about 20 percent.

Decreasing the water-content below 20 percent leads to a gradual fading out of the crystalline x-ray pattern and a corresponding increase in the diffuse background scattering. After strong drying only diffuse scattering is observed.

All these changes are readily reversible. The following explanation is suggested:

The phosphate groups, being the most polar part of the structure would be expected to associate with one another and also with the water molecules. Phosphate-phosphate bonds are considered to be responsible for intermolecular linking in the crystalline structure. The water molecules are grouped around these bonds (approximately four water molecules per phosphorus atom). Increased water content weakens these bonds and leads, first, to a less highly ordered structure and, ultimately, to gel formation and solution. Drying leaves the phosphate-phosphate links intact but leads to the formation of holes in the structure with resulting strain and deformation. The three-dimensional skeleton is preserved in distorted form and crystalline order is restored when the humidity is again increased.

(b) *The Cylindrically Symmetrical Patterson Function*: It was apparent that the

crystalline form was based on a face-centered monoclinic unit cell with the *c*-axis parallel to the fibre axis. But it was not found possible, by direct inspection, to allot all the lattice parameters accurately and unambiguously. To obtain the unit cell with certainty the cylindrically symmetrical Patterson function was calculated. This function is periodic in the fibre-axis direction only.

Special techniques were developed for the measurement of the positions and intensities of the reflections. This was necessary, firstly because all measurements had to be made on micro-photographs, and secondly because the observed reflections were of a variety of shapes and sizes so that integrated intensities could not be directly measured.

On the Patterson function obtained, the lattice translations could be readily identified. On the basis of a unit cell defined by

$$\begin{aligned}a &= 22.0 \text{ \AA} \\b &= 39.8 \text{ \AA} \\c &= 28.1 \text{ \AA} \\\beta &= 96.5^\circ\end{aligned}$$

the 66 independent reflections observed could all be indexed with an error of less than 1 percent.

A very satisfactory confirmation of the correctness of the unit cell and the indexing was provided by a fortunate accident which it has so far not been possible to reproduce. One fibre was obtained which gave a photograph showing strong double orientation. It was found that in this photograph those spots which had been indexed *hkl* were strongest in one pair of quadrants while those indexed *hkl* were strongest in the other pair.

(c) *The Three-Dimensional Patterson Function*: Having established the unit cell with certainty, it is now possible to calculate Patterson sections in the normal way. Work on these is in progress.

In Dr. M. F. Perutz's letter, extracts from a Medical Research Council report are published for the first time. For those interested in the history of the early x-ray studies of DNA at King's college, I give here the main facts which form the background to the report.

Early in 1951 "A" patterns of DNA and very diffuse "B" patterns from DNA and from sperm heads indicated (as I described at a meeting at Cambridge in 1951) that DNA was helical. Shortly afterward, when Rosalind Franklin began experimental work on DNA, she almost immediately obtained (in September 1951) the first clear "B" patterns [described at a seminar in 1951 and published in 1953 (1)]. By the beginning of 1952 I had obtained basically similar patterns from DNA from various sources and from sperm heads. The resemblance (2) of the "B" patterns of DNA and those of

sperm was very clear at that time. The helical interpretation was very obvious too, and it was proposed in general terms in Franklin's fellowship report (3). The "B" patterns of DNA that I obtained at that time were quite adequate for a detailed helical interpretation. This was given later (4), with one of the patterns, alongside the Watson and Crick description (5) of their model. The best, and most helical-looking "B" pattern, was obtained by Franklin in the first half of 1952 and was published in 1953 (6), also with a helical interpretation and alongside the Watson-Crick paper. Confusion arose because, during the summer of 1952, Franklin presented, in our laboratory, "A"-type data (in three dimensions) which showed that the DNA molecule was asymmetrical and therefore nonhelical. Later in the year I wrote for the Medical Research Council report a summary of the DNA x-ray work as a whole in our laboratory. Since our previous emphasis had been entirely on helices, I drew attention in the report to the nonhelical interpretation. In 1953, after the Watson-Crick model had been built and when we had more precise "A" data, I reexamined the question of DNA being nonhelical and found that the data gave no support for the molecule being nonhelical (7).

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References

1. R. E. Franklin and R. G. Gosling, *Acta Cryst.* **6**, 673 (1953).
2. M. H. F. Wilkins and J. T. Randall, *Biochim. Biophys. Acta* **10**, 192 (1953).
3. A. Klug, *Nature* **219**, 808 (1968).
4. M. H. F. Wilkins, A. R. Stokes, H. R. Wilson, *ibid.* **171**, 738 (1953).
5. J. D. Watson and F. H. C. Crick, *ibid.*, p. 737.
6. R. E. Franklin and R. G. Gosling, *ibid.*, p. 740.
7. M. H. F. Wilkins, W. E. Seeds, A. R. Stokes, H. R. Wilson, *ibid.* **172**, 759 (1953).

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I am very sorry that, by not pointing out that the Randall report was non-confidential, I portrayed Max Perutz in a way which allowed your reviewer [*Science* **159**, 1448 (1968)] to badly misconstrue his actions. The report was never marked "confidential," and I should have made the point clear in my text [*The Double Helix* (Athenum, New York, 1968)]. It was my intention to reconstruct the story accurately, and so most people mentioned in the story were given the manuscript, either in first draft or in one of the subsequent

revisions, and asked for their detailed comments.

I must also make the following comments.

1) While I was at Cambridge (1951–53) I was led to believe by general lab gossip that the MRC (Medical Research Council) Biophysics Committee's real function was to oversee the MRC–King's College effort, then its biggest venture into pure science. I regret that Perutz did not ask me to change this point.

2) The Randall report was really very useful, especially to Francis [Crick]. In writing the book I often underdescribed the science involved, since a full description would kill the book for the general reader. So I did not emphasize, on page 181, the difference between "A" and "B" patterns. The relevant fact is not that in November 1951 I *could have* copied down Rosalind's seminar data on the unit cell dimensions and symmetry, but that I *did not*. When Francis was rereading the report, after we realized the significance of the base pairs and were building a model for the "B" structure, he suddenly appreciated the diad axis and its implication for a two-chained structure. Also, the report's explicit mention of the "B" form and its obvious relation to the expansion of DNA fiber length with increase of the surrounding humidity was a relief to Francis, who disliked my habit of never writing anything on paper which I hear at meetings or from friends. The fiasco of November 1951 arose largely from my misinterpretation of Rosy's talk, and with my knowledge of crystallography not really much solidier, I might have easily been mistaken again. Thus the report, while not necessary, was very, very helpful. And if Max had not been a member of the committee, I feel that neither Francis nor I would have seen the report; and so, it was a fluke that we saw it.

3) Lastly, Max's implication that the King's lab was generally open with all their data badly oversimplifies a situation which, in my book, I attempted to show was highly complicated in very human ways.

All these points aside, I regret and apologize to Perutz for the unfortunate passage.

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