STRUCTURAL HELIX

Istvan Hargittai and Magdolna Hargittai

The authors place the discovery of helicity of biological macromolecules in a historical context and enhance the visibility of the role of the mathematician Harry Bateman and the physicist Horace R. Crane in it.

When J. Desmond Bernal for the first time produced a diffraction pattern in an experiment by shining X-rays onto a protein sample in the 1930s, he wandered for hours at night in the streets of Cambridge. The thought kept him sleepless that one day it will be possible to determine the structure of proteins and get closer to uncovering the secret of life. Some of the world's best crystallographers, among them Linus Pauling in Pasadena and W. Lawrence Bragg, Max Perutz, and John Kendrew in Cambridge, UK, worked toward this goal.

Already in the early 1930s, William T. Astbury and his group found two forms of the polypeptide chain, the extended beta-pleated sheet and the coiled alpha-keratin. Pauling chose to work on alpha-keratin. His strategy was first to predict the dimensions of the polypeptide chain using his knowledge of structural chemistry. Then, he planned to examine the possible conformations of the chain to identify those that agreed with the X-ray diffraction data. The principal information, which was possible to obtain from the rather fuzzy diffraction patterns of alpha-keratin was that the structural unit repeated in 5.1 angstrom along the axis of the chain. This would require at least two amino acid residues for this repeat distance.

Pauling had an advantage in narrowing down the problem because he knew that the carbon to nitrogen bond was much shorter than a single bond, had a considerably double-bond character, and the peptide bond configuration, the C-N bond and the four adjacent atoms, was planar or nearly planar. This knowledge came from the determination of the geometry of simple molecules and the application of the theory of resonance. Still, he was unable to find a satisfactory solution in the late 1930s. He decided that he needed still more information on the geometry of the individual building blocks of the polypeptide chain. Accordingly, he initiated a series of structure determination for simple molecules. For a while he was engaged in other studies during World War II.

Pauling had excellent graduate students and for some time each was supposed to determine the structure of a simple molecule either by X-ray crystallography or gas-phase electron diffraction. He did not order them to choose such a project, but he had his ways of making them prefer it. Matthew Meselson the future Harvard professor was one of Pauling's graduate students already after the war, but his description of choosing his graduate project may characterize the general situation. We quote him on this story [1]:

I became his [Pauling's] graduate student. The first time he gave me a problem he took a rock and he put it on my desk, and we had a conversation, which went something like this:

– Matt, do you know about tellurium?

– Yes, Professor Pauling.

– It's under selenium and sulfur in the periodic chart of the elements.

– Yes, Professor Pauling.

– Have you ever smelled hydrogen sulfide?

– Yes, Professor Pauling.

– It smells bad, doesn't it?

– Yes, Professor Pauling.

– Have you ever smelled hydrogen selenide?

– No, Professor Pauling.

– Well, it's much worse.

– I see, Professor Pauling.

– Now, Matt, have you ever smelled hydrogen telluride, you probably have not.

– No, Professor Pauling.

– It's much worse than hydrogen selenide as hydrogen selenide is much worse than hydrogen sulfide.

– I see, Professor Pauling.

– The reason I'm telling you this, Matt, is that I want you to work with the crystal structures of some salts of tellurium, but I want you to be very careful because some chemists had gotten tellurium into their system, and they acquired something called tellurium breadth. It'd isolate you from society because it's so bad. Some of these people have committed suicide. But I know you'd be very careful. So, what do you think?

– I'd like to go home and think about it.

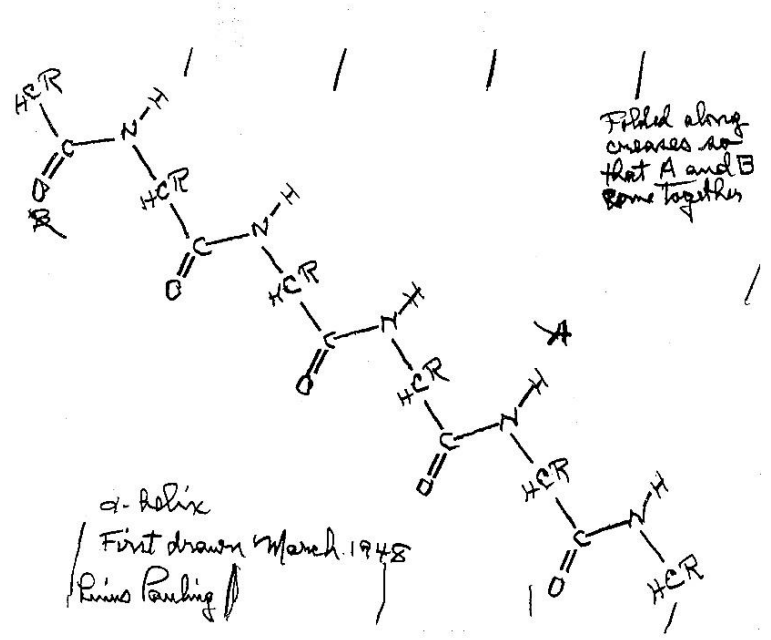
When I came back, I told him that I was really interested in biology, and I asked him to give me a molecule with some carbons and hydrogens and nitrogens. He laughed. I think he may have pulled this trick on other students too. I don't think he was serious, but I don't really know. So, I did a crystal structure with two amide groups to prove what he'd already proven that the peptide bond is planar because of resonance. He was a wonderful teacher.

Pauling returned to the structure of the peptide chain a decade later, in 1948, while he was on sabbatical in Oxford. He introduced some simplifying assumptions for the chain in order to facilitate the elucidation of its structure. He disregarded the differences in the amino acids building up the polypeptide chain; instead, he considered them structurally equivalent with respect of folding the chain, thereby introducing a helpful symmetry approach in his analysis.

Ava and Linus Pauling. Photograph by and courtesy of the late Karl Maramorosch

The next step was when he remembered a course of mathematics by the English mathematician Harry Bateman (1882–1946) that he attended 25 years before in Pasadena. Bateman studied in Manchester and earned higher qualifications in Cambridge. He studied also in Göttingen and Paris, taught in Liverpool and Manchester in England and at Bryn Mawr College and Johns

Hopkins University in the United States. He joined what then was Throop Polytechnic Institute in 1917, which changed its name in 1920 to California Institute of Technology. According to Pauling [2], he learned from Bateman that the most general operation that converts an asymmetric element, for example, an amino acid, into an equivalent asymmetric element, is a rotation-translation, that is, a rotation around an axis combined with a translation along the axis, and that such an operation produces a *helix*. Accordingly, Pauling took the polypeptide chain, rotated around the two single bonds to the alpha carbon atom, with the amount of rotation being the same from one peptide group to the next, and on and on and on. He kept the peptide groups planar with the proper dimensions and searched for a structure in which each NH group formed a hydrogen bond with a carbonyl group.



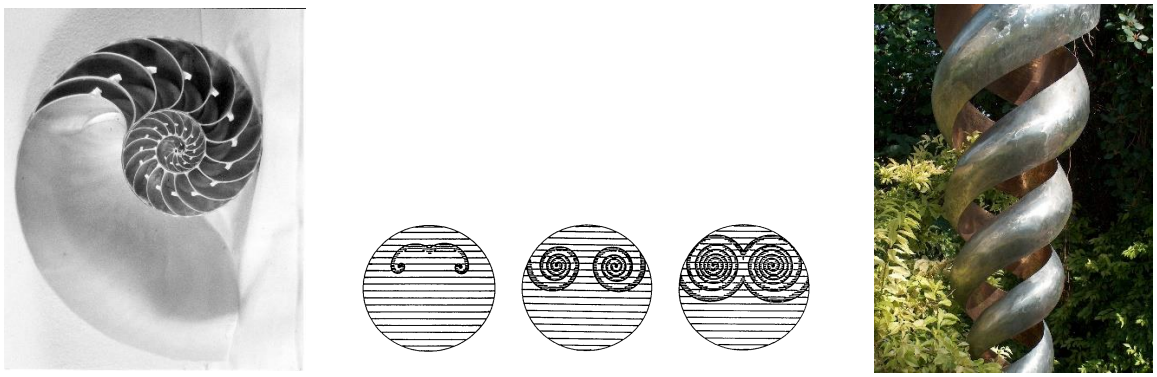
Left: Linus Pauling's drawing of the stretched alpha-helix structure, March 1948 (Ref. 2)

Pauling sketched a polypeptide chain on a piece of paper and folded it along parallel lines. Two structures satisfied his assumptions. One of them he named alpha-helix with 4.6 residues per turn. There was only one disturbing observation that the corresponding repeat distance was 5.4 angstroms rather than 5.1 (mentioned above). However, this discrepancy did not deter Pauling from proceeding because he believed that his model was right. Eventually, he, and independently Francis Crick, interpreted this discrepancy by some slight additional coiling of the helices, which facilitated to achieve closest packing. Crick considered the discrepancy and its interpretation a nice example of symmetry breaking by a weak interaction [3]. Pauling and his associates published the alpha-helix structure in two papers [4 and 5]. In the meantime, Bragg, Kendrew, and Perutz of Cambridge, UK, also published their paper on the structure of alpha-keratin [6]. They described about 20 structures and none of them was correct. They did not utilize the chemical knowledge of the planarity of the peptide group.

At this point we interrupt our description of events to comment on Reference 2. It is a paper by Pauling published posthumously. The gist of its story, following Dorothy Munro's narrative [2], is this: In 1982, Pauling produced a manuscript titled "The Discovery of the Alpha Helix" at the request of W.H. Freeman and Company as a chapter for a book by Donald Voet (it must have been the biochemistry textbook, which has been in print ever since). Pauling died in 1994 and as his long-time former secretary/assistant Dorothy Munro found out in 1995 that the chapter had not been

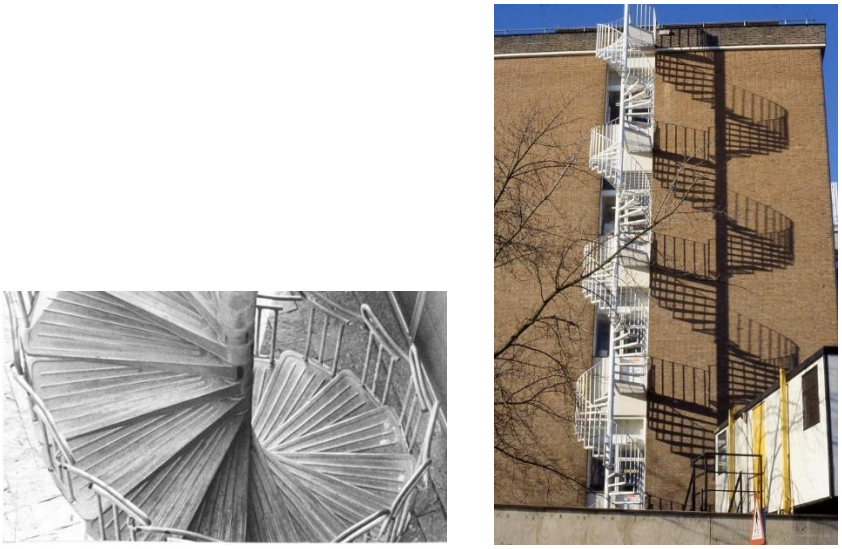
included in the book. Munro was looking for a venue to bring out the paper. Robert Paradowski, Pauling's authorized biographer, suggested to her the *Chemical Intelligencer*, the recently launched magazine about the culture of chemistry. One of us (IH) was the founding editor of the magazine, which was happy to publish the manuscript [2]. We have asked Donald Voet whether he might add anything to this story. He remembered that the editor of the book asked Pauling to write the chapter, but as far as he knew, nothing further happened—he responded to our query [7].

Coming back to the discovery of alpha helix, there was a noteworthy difference in the titles of the two Pauling papers in 1950 [4] and 1951 [5]. The first used the word "spiral," and the second, "helix." Even seventy years later these two words appear interchangeably although, strictly speaking only "helix" is correct for these structures.



Examples of spirals. Left: Nautilus shell. Photograph by and courtesy of Lloyd Kahn [8]. Reproduced with permission. Middle: The evolution of a spiral ring pattern in time, from left to right, in a Belousov-Zhabotinsky oscillating reaction [9]. Right: Double spiral (detail), "The Inner Light" by Gidon Graetz, in the garden of the Weizmann Institute in Rehovot, Israel. Photograph by the authors

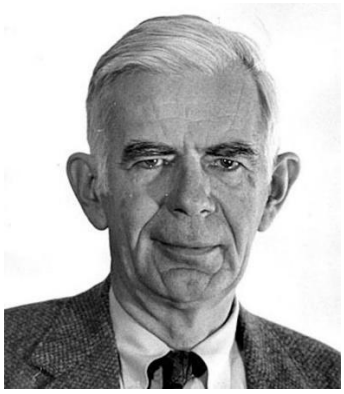
Spirals have changing diameters whereas the diameter of a helix is constant. Hence, the structure of biological macromolecules is properly described as helical. In everyday speech, helical constructions are often referred to as spiral; examples include the spiral notebook and the spiral staircase. For the latter we present two examples. We would not suggest trying to change the every-day usage of spiral notebook or staircase, but in technical texts, it is proper to stick to helix for describing the structure of large biological molecules.



Helical structures of "spiral" staircases, both photographs by the authors. The one on the right, the

spiral staircase and its shadow make it a *doubled* helix (though not a *double* helix). It is outside the wall of the former (until 2013) headquarters of the MRC Laboratory of Molecular Biology

As is seen in the titles of Refs. 4 and 5, Pauling also had to learn the difference between spiral and helix. Jack D. Dunitz first met Pauling in the winter of 1947-1948 during Pauling's visiting professorship in Oxford. Then, Dunitz stayed in Pauling's group at Caltech, 1948–1951, so he could follow closely the discovery of the alpha-helix structure. When Pauling talked to Dunitz about his models, he used the term "spiral." At one point, Dunitz pointed out to Pauling that "helix" would be the right term in this case. According to Dunitz, henceforth, Pauling used the term "helix" consistently. Dunitz liked to think that he helped to give the alpha-helix its name—he considered this to be his personal contribution to molecular biology [10].



Horace R. Crane (Horace R. Crane - National Science and Technology Medals Foundation (nationalmedals.org))

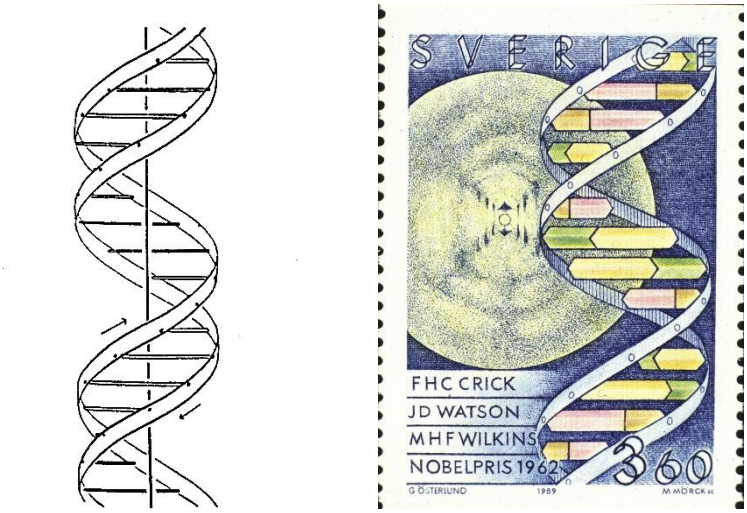
We learned from Donald Caspar [11] that the nuclear physicist Horace R. Crane (1907–2007) was the first to suggest the idea that assemblies of identical units build helical structures [12]. Crane spent his long career as Professor of Physics at the University of Michigan. In 1986, he received the National Medal of Science "For the first measurement of the magnetic moment and spin of free electrons and positrons." In World War II, he helped to develop radar at MIT and worked on the proximity fuse at the Carnegie Institution and at the University of Michigan. Less well known is that he also worked on problems of assembly line operation. After the war, this experience led him to recognize the analogy of assembling biological structures to a subassembly manufacturing process [13].

Here we quote Caspar about what Crane did: "He built simple models out of matchboxes, for example, sticking matchboxes together in the same way, arriving at a helix naturally by using the same pair-wise connections repeatedly. He recognized that there is no requirement for the screw symmetry to be rational, that is, that the helix have an integral number of units in some integral number of turns. Such an arrangement in which the unit axial translation is not rationally related to the helix pitch is nowadays called incommensurate periodicity by physicists." [13]

W. Cochran, Francis Crick, and V. Vand worked out the theory of diffraction of helical structures [14]. Initially, they considered a thin helical wire, then, a set of identical point atoms spaced at regular intervals on a helix, and finally the polypeptide helix based on the Pauling alpha-helix model.

Entrance to 19-20 Portugal Place, the former home of Francis and Odile Crick in Cambridge, UK. Photograph by the authors

Crick had the single helix (rather than a double helix) in mind when he accorded the name "Golden Helix" his Cambridge home. He erected a simple metallic helix above its entrance, painted yellow. The Nobel laureate Arthur Kornberg published a book about biotechnology ventures, and he titled it The Golden Helix. He used this expression for the double helix and the meaning of the title was made unambiguous when he wrote in the preface of the book: "Turning the DNA helix into gold seemed another alchemist dream" [15].

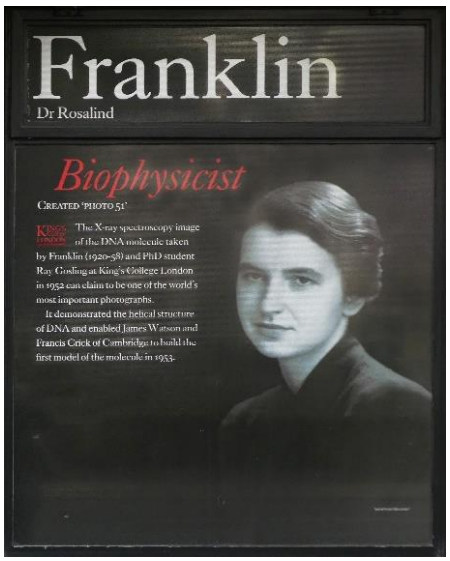


Schematic representations of the DNA double helix in the original *Nature* paper (left) and on a Swedish postage stamp (right). The model on the postage stamp hints at the linked bases somewhat more in detail than the more schematic drawing on the left. The backdrop on the postage stamp represents the famous photograph No 51 of the DNA diffraction patterns recorded by Rosalind Franklin and her student, Raymond Gosling, without displaying their names


Left: Odile and Francis Crick, 2004, in their home in La Jolla (photograph by the authors)
Right: James D. Watson, 2000, in the Hargittais' home in Budapest (photograph by the authors)

Our mention of Kornberg's book already brought us to the double helix structure of DNA. Initially, James D. Watson and Francis Crick suggested the double-helix structure for DNA in their one-page seminal *Nature* paper in 1953 [16]. This brief report was illustrated by a schematic drawing of the double helix majestic in its simplicity (see above). For a long time, we supposed that Odile Crick had drawn it, perhaps this stemmed from our romanticizing the story and the knowledge of her artistic inclination. In 2004, when we visited the Cricks, we asked them about the origin of the drawing. We were taken aback when we learned that Odile Crick did not play any role in producing this illustration; it was prepared after some other cartoon simply by tracing its contour lines.

The first seminal paper containing the suggestion for the double-helix structure, soon followed by a second, somewhat longer note. It elaborated the genetic implications of the double-helix structure [17]. Watson and Crick must have liked the purely diagrammatic figure quoted above because they reproduced it in this second paper. From the two Watson-Crick papers it is not obvious that there were four antecedents to their discovery [18]: "One was the discovery of Oswald Avery and his two co-workers that DNA is the substance of heredity [19]. The second was Erwin Chargaff's observation that the purine and pyrimidine bases occur in a 1:1 ratio in the DNA of all organisms [20], which came to be expressed as base-pairing in the Watson–Crick model. The third was Linus Pauling's discovery of the alpha-helix [5] of protein structure in which he showed the helicity of a biological macromolecule. The fourth was Rosalind Franklin's careful X-ray diffraction measurements of DNA [21], which, among others, pointed to the C_2 symmetry of the structure."



Left: Photograph 51 of the X-ray diffraction pattern of DNA by Rosalind Franklin and Raymond Gosling on the mural by Larry Kirkland in the lobby of the Keck Center, 500 5th Street NW in Washington, D.C. The center serves as the offices of the three U.S. national academies: the National Academy of Sciences, the National Academy of Engineering, and the National Academy of Medicine. Photograph by the authors Right: Rosalind Franklin's portrait in a window display at King's College, London. Photograph by the authors

The C_2 symmetry has a special importance in the double-helix structure of DNA [18]: "The importance of the knowledge of C_2 symmetry, which came from the X-ray patterns, was not explicitly acknowledged in Watson and Crick's communications, which is the more curious because the double-helix structure could have been described in a simplified way stressing the presence of this symmetry. … Of Watson and Crick, Watson gave much less importance to C_2 symmetry than Crick, perhaps because Watson had no background in crystallography. Furthermore, knowing that Watson had very little faith in the importance of Chargaff's observations, it is remarkable how far he advanced in his intuitive model-building. Crick, on the other hand understood the implications of C_2 symmetry and when they arrived at the concept of base-pairing, he pointed out that the base pair implied a twofold axis in the planes of the bases, perpendicular to the axis of the helices. In other words, the two chains were anti-parallel [22]."

Horizontal double helix as part of the fence at a pub near the Cricks' former home, "The Maypole," 20A Portugal Place. Photographed in 2000 by the authors

The Golden Helix at the Cricks' former residence is right-handed (see above) as is DNA, but the double helix of the fence outside the pub is left-handed [23]. The handedness of the helix in the

fence was a mistake by the landlord of the pub who commissioned it after receiving the dimensions from Crick, who was a regular visitor to the pub. The double-helix model has become a popular icon so widespread that today it is one of the best-known, if not *the* best-known symbol of science. It is a winner especially if contrasted with another icon, the mushroom cloud of the nuclear explosions. Not everybody was pleased though by the success of this model. Erwin Chargaff, whose discovery of base-pairing in DNA was a crucial ingredient in making the discovery of the double helix [18], wrote disparagingly about what he considered to be a propaganda campaign for the model [24].

Erecting a sculpture is not a trivial matter, yet double-helix memorials abound. We have selected four examples for presentation.

Left: Sculpture of the double helix by Bror Marklund, 1997, in front of the medical school of Uppsala University. Photograph by the authors
Right: “Temple of Wisdom” by Marino Di Prospero, 2002, on the campus of the University of L’Aquila. Photograph by the authors

The Uppsala sculpture is large and beautiful. At the top end it splits as if getting ready for reproduction. At closer scrutiny, what might be the bases appear outside of the backbone. This erroneous arrangement was also in one of Pauling’s models when he somewhat belatedly joined the race for the DNA structure. But on the artist’s part this may have been an expression of artistic freedom or the consequence of a misunderstanding. The elegance of the L’Aquila sculpture comes from its material being white Carrara marble. Here, also, the top end splits.

Double-helix sculpture by Tom Otterness, 2001, in the sculpture garden at Battery Park City in Lower Manhattan, New York. Photograph by the authors

Matthew Meselson and Franklin Stahl, many years after their seminal experiment performed at Caltech. Courtesy of Franklin Stahl

The Manhattan double-helix sculpture not only splits at the top end; the split threads are already forming new double helices. To us it meant also the representation of the beautiful Meselson-Stahl experiment in which Matthew Meselson and Franklin Stahl demonstrated the semiconservative mechanism of DNA replication [25]. It has been called “the most beautiful experiment in biology” [26].

“Spirals Time—Time Spirals” by Charles A. Jencks at the Cold Spring Harbor Laboratory with the residence of James D. and Elizabeth L. Watson in the background. Photograph by the authors. The top end of the Cold Spring Harbor Laboratory sculpture may have caused a problem to the sculptor hence the awkward solution.

George Gamow with a model of the double helix. Courtesy of the late Igor Gamow, George Gamow’s son

Model making was an indispensable component of the discoveries of alpha helix by Pauling and of the double helix by Watson and Crick. It was a finely choreographed spectacle when Pauling introduced his model in a public presentation in Pasadena. The alpha-helix model was hiding under a cover until the right moment when Pauling, like a magician, removed the cover and the audience gasped at its magnificence. Soon after the publications on the DNA structure in *Nature*, the great physicist George Gamow turned to Watson and Crick raising the question of information transfer from nucleic acids to proteins. He was one of the initiators of the search for the genetic code though the molecular biologists like to stress the factual errors in his ideas rather than recognizing their fruitfulness. He was also a model builder.

Left: James D. Watson with the double-helix model in his left hand at the Cold Spring Harbor Laboratory, June 1953. Photograph by and courtesy of the late Karl Maramorosch

Watson presented his double-helix model of modest size to a June 1953 meeting at the Cold Spring Harbor Laboratory, that is, soon after the discovery was published in *Nature* in April. There was an impact, and the consequences reverberate to this date. The MRC Laboratory of Molecular Biology developed an art of model making following Pauling's example and soon it had a full room of models. During the search for the structure of DNA it was not yet obvious that they were dealing with a model of historic importance. Eventually, it was not easy to assemble the parts of the original model to be exhibited in the Science Museum in London [27], but it is there today as a milestone in science history.

Istvan Hargittai and Magdolna Hargittai are at Budapest University of Technology and Economics

LITERATURE

[1] Istvan Hargittai and Magdolna Hargittai, *Candid Science VI: More Conversations with Famous Scientists*. Singapore: World Scientific, 2006, Chapter 3, "Matthew Meselson, 40–61; actual quote, pp. 58–59.

[2] Linus Pauling, "The Discovery of the Alpha Helix." *Chem. Intell*. 1996, 2(1), 32–38. This was communicated by the late Linus Pauling's former secretary/assistant, Dorothy Munro. It was reproduced in B. Hargittai and I. Hargittai, eds., Culture of Chemistry: The Best Articles on the Human Side of 20th-Century Chemistry from the Archives of the Chemical Intelligencer. New York: Springer, 2015, pp. 161–167. For a detailed discussion, see, Istvan Hargittai and Magdolna Hargittai, *In Our Own Image: Personal Symmetry in Discovery*. New York: Kluwer Academic/Plenum Publishers, 2000, Chapter 5, "Linus Pauling," pp. 82–111.

[3] Francis Crick, *What Mad Pursuit: A Personal View of Scientific Discovery*. Basic Books, New York, 1988, p. 59.

[4] L. Pauling and R.B. Corey, "Two Hydrogen-Bonded Spiral Configurations of the Polypeptide

Chain." *J. Am. Chem. Soc*. 1950, 72, 5349 (1 page)

[5] L. Pauling, R.B. Corey, and H.R. Branson, "The Structure of Proteins: Two Hydrogen-Bonded Helical Configurations of the Polypeptide Chain." *Proc. Natl. Acad. Sci. USA* 1951, 37, 205–211

[6] W.L. Bragg, J.C. Kendrew, and M.F. Perutz, "Polypeptide Chain Configuration in Crystalline Proteins." *Proc. R. Soc*. 1950, 203A, 321–357

[7] E-mail exchange with Donald Voet (University of Pennsylvania), December 27, 2022.

[8] I. Hargittai and M. Hargittai, *Symmetry: A Unifying Concept*. Bolinas, California: Shelter Publications, 1994; Figure: p. 163

[9] E. Körös, "Oscillations, Waves, and Spirals in Chemical Systems." In I. Hargittai and C.A. Pickover, eds., *Spiral Symmetry*. Singapore: World Scientific, 1992, pp. 221–249; Figure 10: p. 241

[10] I. Hargittai, "Jack D. Dunitz (1923–2021): a chemists' crystallographer." *Struct. Chem*. 2022, 33, 291–297.

[11] I. Hargittai, "Donald L. Caspar (1927-2021)—pioneer of virus structures." *Struct. Chem*. 2022, 33, 993–995.

[12] H. R. Crane, "Principles and Problems of Biological Growth." *Sci. Month*. 1950, 70, 376–389; H.R. Crane, "Biological Growth." In Donald B. Wetlaufer, *The Protein Folding Problem*. New York: Routledge, 1984, Chapter 8.

[13] For extensive excerpts from an unpublished conversation with Donald Caspar, 1996, in Tallahassee, Florida, 1996, see Istvan Hargittai and Magdolna Hargittai, *In Our Own Image: Personal Symmetry in Discovery*. Kluwer Academic/Plenum Publishers, 2000. The actual quote is in p. 93.

[14] W. Cochran, F.H.C. Crick, and V. Vand, "The Structure of Synthetic Polypeptides. I. The Transform of Atoms on a Helix." *Acta Crystallogr*. 1952, 5, 581–586.

[15] Arthur Kornberg, *The Golden Helix: Inside Biotech Ventures*. University Science Books, Sausalito, California, 1995.

[16] J.D. Watson and F.H.C. Crick, "Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid." *Nature* 1953, 171, 737–738.

[17] J.D. Watson and F.H.C. Crick, "Genetical Implications of the Structure of Deoxyribonucleic Acid." *Nature* 1953, 171, 964–967.

[18] I. Hargittai, "Francis Crick (1916-2004)." *Struct. Chem*. 2004, 15, 545–546.

[19] O.T. Avery, C. MacLeod, and M. McCarty, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III." *J. Exper. Med*. 1944, 79, 137–158.

[20] E. Chargaff, "Chemical specificity of nucleic acids and mechanism of their enzymatic degradation." *Experientia* 1950, 6, 201-209.

[21] R.E. Franklin and R.G. Gosling, “Molecular configuration in sodium thymonucleate.” *Nature* 1953, 171, 740–741.

[22] F. Crick, Private communication by letter, 2003.

[23] I. Hargittai and M. Hargittai, “A Unique Venue of Discoveries in Structural Chemistry: the 75-Year and 60-Year Jubilees of the MRC Laboratory of Molecular Biology—A Personal Tribute.” *Struct. Chem*. 2022, 33, 281–289.

[24] E. Chargaff, *Heraclitean Fire: Sketches from a Life before Nature*. The Rockefeller University Press, New York, 1978, 106.

[25] Matthew Meselson and Franklin Stahl, “The Replication of DNA in *Escherichia Coli*.” *Proc. Natl. Acad. Sci*. 1958, 44(7), 671–682.

[26] F.L. Holmes, *Meselson, Stahl, and the Replication of DNA: A History of “The Most Beautiful Experiment in Biology”*. New Haven and London: 2001.

[27] I. Hargittai and M. Hargittai, *Science in London: A Guide to Memorials*. Springer Nature, 2021.