STANDING ON THE SHOULDERS OF GIANTS: JAMES WATSON, FRANCIS CRICK, MAURICE WILKINS, ROSALIND FRANKLIN AND THE BIRTH OF MOLECULAR BIOLOGY

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In the 20th century, DNA became a magnet, attracting representatives of various sciences. Prominent researchers competed among themselves to discover the structure of DNA and to explain the mechanisms that determine our “natural fate”, i.e., our heredity. An American chemist, biochemist, chemical engineer Linus Pauling, a British physicist and molecular biologist Maurice Wilkins, a British chemist, biophysicist, and X-ray crystallographer Rosalind Franklin, an American geneticist, molecular biologist, zoologist James Watson, a British molecular biologist, biophysicist, and neuroscientist Francis Crick were among them. They searched for the scientific explanation for the enigma of life hidden in DNA. An accurate description of DNA double-helical structure belongs to James Watson and Francis Crick. However, the missing pieces of the puzzle were elaborated by Rosalind Franklin, who was not given enough credit for her dedicated scientific work. Unlike her, Francis Crick, James Watson, and Maurice Wilkins were awarded the Nobel Prize in Physiology or Medicine 1962 for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material. Whatever the DNA story is, it shows that all great scientific discoveries are not made from scratch. The immense number of people have contributed to the development of science and literally every researcher stands on the shoulders of giants, while the idea itself is in the air. The discovery of the structure of DNA became a cornerstone for the new scientific paradigm – biology acquired a molecular and biochemical basis.

Key words: DNA, DNA double helix, James Watson, Francis Crick, Rosalind Franklin, Maurice Wilkins, the Nobel Prize in Physiology or Medicine 1962.

Since time immemorial, humans have tried to understand whether they have free will or there is a predestined fate. Why are some born beautiful, healthy, and smart, while others have to eke out a miserable existence on the sidelines of a happy life? Who is to blame for this: sinful parents, own karma, or pure chance? Humans embrace both natural and cultural worlds being deeply rooted in each of them [1]. While in the world of culture (the world of symbols) people have freedom of choice, in the world of nature they have to obey its laws. Only by realizing the laws of nature and considering them, a person becomes free. What natural mechanisms determine our “natural fate”, i.e., our heredity? This question has long been asked by many scientists who have tried to explain the genetic patterns. Information about a living creature is encoded in the genes, and the carrier of all human or animal genes is DNA – deoxyribonucleic acid.

DNA as a molecule located in the nucleus of a living cell was discovered in the 1860s by the Swiss physician F. Miescher [2]. In 1879, a German biologist and a founder of cytogenetics W. Flemming discovered chromatin (later known as chromosomes).
within the nucleus [3]. The key role played by chromosomes was revealed in the course of studies on cell division. Further analysis suggested that chromosomes contained DNA, and a German zoologist O. Hertwig recognized the role of the cell nucleus during inheritance and chromosome reduction during meiosis. In 1885, he wrote that nuclein, which was later called nucleic acid, is the substance responsible not only for fertilization, but also for the transmission of hereditary characteristics [4]. “By 1900, it was known that the basic building blocks of DNA were phosphate, a sugar (later shown to be deoxyribose) and four heterocyclic bases – two of which were purines [adenine (A) and guanine (G)] while the other two were pyrimidines [cytosine (C) and thymine (T)]” [5]. In the 1930s, Swedish cytologist and geneticist T. Caspersson and Swedish biochemist E. Hammersten showed that DNA is a polymer [6].

In 1935, N.W. Timoféeff-Ressovsky, K.G. Zimmer and M. Delbrück suggested that chromosomes were large molecules, and their structure could be changed by X-rays and thus, it was possible to change the heritable characteristics ruled by these chromosomes [7]. O. Avery, C. Macleod, and M. McCarty – medical microbiologists at the Rockefeller Institute in New York – in their paper published in 1944 described the experiment that isolated DNA as the material of which genes and chromosomes are made. They identified DNA as the transforming principle (genes) [8].

Physicist E. Schrödinger also contributed to this discovery [9]. He suggested the idea of a genetic code and argued that the genetic material had to have a non-repetitive molecular structure. Considering a molecule as a solid – a crystal, Schrödinger claimed: “We believe a gene – or perhaps the whole chromosome fibre – to be an aperiodic solid” [10]. This aperiodic crystal forms the hereditary substance.

A famous Austrian-American biochemist E. Chargaff introduced two rules that eventually led to the discovery of the double helix structure of DNA. He noticed that DNA contained equal amounts of adenine and thymine and equal amounts of cytosine and guanine. This idea contributed to the understanding of the chemical pairings that make up the double helix. E. Chargaff found that amount of guanine, cytosine, thymine and adenine vary with the species, which means that DNA is the genetic material for life [11].

X-ray crystallography contributed greatly to the discovery of DNA. In 1938, an English physicist and molecular biologist W. Astbury and his research assistant E. Beighton had obtained X-ray image of DNA. It was a year before an English chemist and X-ray crystallographer R. Franklin took her incredibly famous Photo 51, which “showed a pattern of black spots arranged in the shape of a cross, formed when X-rays were diffracted by fibres of DNA” [12]. W. Astbury helped to develop the methods used by R. Franklin and M. Wilkins, as well as made early studies of the DNA molecule and paved the way for J. Watson and F. Crick’s scientific discovery. In so far as “winner takes it all”, the name of W. Astbury was undeservedly forgotten. K. Hall, the author of “The Man in the Monkeynut Coat” [13], emphasizes, “Astbury’s name is today largely unknown except to a select group of historians of science” [14].

William Astbury [15]

DNA has become a magnet attracting representatives of various sciences. In the 1950s, there were three groups of researchers aimed at determining the structure of DNA. The first group at King’s College, London, was led by M. Wilkins. R. Franklin joined this group later. They examined X-ray diffraction patterns of DNA fibers. Cambridge was represented by F. Crick and J. Watson. They were focused on building physical models. Caltech group was led by L. Pauling who discovered that many proteins included helical shapes [6, 16]. Later L. Pauling was twice awarded the Nobel Prize: the first award in 1954 recognized “his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances” [17], the second award in 1962 – “for his opposition to weapons of mass destruction” [18].

However, an accurate description of DNA double-helical structure belongs to his more successful competitors J. Watson and F. Crick. In fact, the contemporary story of DNA began in 1953.
James Watson (James Dewey Watson), a prominent American geneticist, molecular biologist, zoologist, was born on April 6, 1928 in Chicago, USA. Being a bright and inquisitive child, he attended Horace Mann Grammar School and South Shore High School. At the age of 15, he earned a scholarship to the University of Chicago and enrolled in the university [20]. He received his Bachelor of Science degree in zoology in 1947 and attended Indiana University. Here in 1950, he received his PhD in zoology. After reading E. Schrödinger’s book “What Is Life? The Physical Aspect of the Living Cell”, J. Watson decided to study genetics. He was fascinated by the idea that the secret of life is hidden in genes and chromosomes. J. Watson wrote: “This book very elegantly propounded the belief that genes were the key components of living cells and that, to understand what life is, we must know how genes act” [21].

Based on his virus research and Avery’s experiments, J. Watson came to the conclusion that gene could be understood after a detailed explanation of nucleic acid molecules. J. Watson was influenced by the work of the geneticists H. J. Muller and T. M. Sonneborn and a microbiologist S. E. Luria who won the 1969 Nobel Prize in Physiology or Medicine for his work on the Luria–Delbrück experiment, which concerned the nature of genetic mutations.

In 1950, J. Watson began his postdoctoral studies in Copenhagen as a Merck Fellow of the National Research Council. He studied bacterial viruses to investigate the structure of DNA. In 1951, he met Maurice Wilkins – a New Zealand-born British physicist and molecular biologist – and saw for the first time a crystalline DNA’s X-ray diffraction pattern. This year, S. Luria and J. Kendrew helped J. Watson move his research to the University of Cambridge’s Cavendish Laboratory, where he continued his work with X-rays, learning diffraction techniques [23]. J. Watson shared his office with a PhD student Francis Crick.

Francis Harry Compton Crick – a distinguished British molecular biologist, biophysicist, and neuroscientist – was born on June 8, 1916, in Northampton, England. He studied at Northampton Grammar School and Mill Hill School, London. Later he enrolled in University College, London, graduating with a Bachelor Degree in 1937. He conducted research for a PhD under Prof. E.N. da C. Andrade, however, his scientific path was interrupted by WWII. During the war, he was involved in military research working as a scientist for the British Admiralty. In 1947, he left the Admiralty to study biology, of which he knew not much at that time [24]. The next few years, he spent learning biology, organic chemistry, and crystallography [25]. His early studies at Cambridge were supported by a studentship from the Medical Research Council (MRC). In 1949, F. Crick joined the MRC unit headed by M. Perutz. During this period, he worked on the X-ray crystallography of proteins. In 1954, he obtained his PhD on a thesis entitled “X-ray diffraction: polypeptides and proteins”. During the
academic year 1953-1954, F. Crick was on a leave of absence at the Protein Structure Project of the Brooklyn Polytechnic in Brooklyn, New York. He also lectured at Harvard as a Visiting Professor [25].

The friendship with J. Watson had a huge impact on F. Crick’s career: “they shared an interest in the fundamental question of how genetic information could be stored in molecular form, leading in 1953 to the proposal of the double-helical structure for DNA” [27].

For about two years J. Watson and F. Crick worked together without success. Emulating L. Pauling, who had made an important but failed effort to describe DNA, they began building three-dimensional models using cardboard cutouts and sheet metal to represent the molecule’s chainlike structure. They were aware that DNA might have the general winding shape of a helix. But it was not clear how adenine, guanine, thymine, and cytosine were arranged around a sugar and phosphate backbone [29]. An unexpected insight came from King’s College group led by M. Wilkins.

Maurice Hugh Frederick Wilkins (1916–2004) was born in New Zealand. His family moved to England when Maurice was 6 years old. He got his education at King Edward’s School, Birmingham. He studied physics at St. John's College, Cambridge, obtaining his degree in 1938. Thereafter, he joined the University of Birmingham, where he investigated the luminescence of solids and earned a PhD in 1940.

After WWII, M. Wilkins lectured at St. Andrews’ University, Scotland. He had spent seven years in physics research and later started exploring biophysics that moved him to King’s College, London, where he became a member of the staff of the Medical Research Council Biophysics Research Unit. He studied genetic effects of ultrasonics, the orientation of purines and pyrimidines in tobacco mosaic virus and in nucleic acids, the arrangement of virus particles in crystals of TMV. Later on, M. Wilkins began X-ray diffraction studies of DNA and sperm heads. Further X-ray studies established the correctness of the Watson – Crick proposal for DNA structure [30].

A key role in determining the structure of DNA belongs to the other member of the King College group – to Rosalind Franklin. Rosalind Elsie Franklin (1920–1958) was a British chemist, biophysicist, and X-ray crystallographer. She was born in London, England. Being exceptionally intelligent, she got her education at Norland Place in West London and St.
Paul’s Girls’ School. Later she entered the University of Cambridge to study chemistry. In 1941, R. Franklin was awarded Second Class Honors in her finals (it was accepted as a bachelor’s degree). Working as an assistant research officer at the British Coal Utilization Research Association, Rosalind studied the porosity of coal. This exploration became the basis of her PhD thesis “The physical chemistry of solid organic colloids with special reference to coal” defended in 1945 [32]. In 1947-1950 she worked with J. Mering at the State Chemical Laboratory in Paris where she studied X-ray diffraction technology. This work led to her research on the structural changes caused by the formation of graphite in heated carbons. In 1951, R. Franklin joined the Biophysical Laboratory at King’s College, London. There she applied X-ray diffraction methods to the study of DNA [33].

Though R. Franklin was not the first to obtain X-ray images of DNA, she managed to take a cardinal step in the right direction. Instead of crystals, Rosalind studied DNA fibers. She faced a very serious difficulty: the photographs were poorly reproduced and unclear. She made a machine, in which she maintained a fixed humidity, and began to change this humidity. She discovered two different forms of DNA molecule – A form (low humidity) and B form (high humidity) [35]. The latter was of the greatest importance, because living cells are characterized by high humidity. One of the “X-ray diffraction pictures of the B form of DNA, known as Photograph 51, became famous as critical evidence in identifying the structure of DNA” [32]. R. Franklin had some ideas on DNA structure, but she had not developed them.

At the beginning of 1953, M. Wilkins without R. Franklin’s permission showed Photo 51 to a competing scientist J. Watson [37]. J. Watson in his book “The Double Helix” put it this way: “since the middle of the summer Rosy (R. Franklin – authors note) had had evidence for a new three-dimensional form of DNA. It occurred when the DNA molecules were surrounded by a large amount of water. When I asked what the pattern was like, Maurice (M. Wilkins – authors note) went into the adjacent room to pick up a print of the new form they called the “B” structure.

The instant I saw the picture my mouth fell open and my pulse began to race. The pattern was unbelievably simpler than those obtained previously (“A” form). Moreover, the black cross of reflections which dominated the picture could arise only from a helical structure. With the A form, the argument for a helix was never straightforward and considerable ambiguity existed as to exactly which type of helical symmetry was present. With the B form, however, mere inspection of its X-ray picture gave several of the vital helical parameters. Conceivably, after only a few minutes’ calculations, the number of chains in the molecule could be fixed” [21].

Based largely on Watson’s memoirs, the “stealing myth” emerged. However, the situation that arose in the scientific community was not so simple – a photograph itself could not shed any light on the chemical structure of the molecule, as well as on the number of strands. J. Watson and F. Crick needed precise observations from X-ray crystallography and they got this data from Franklin’s report given to M. Perutz and from him to L. Bragg, the head of Watson and Crick’s laboratory. Without asking R. Franklin for permission to interpret her
data, F. Crick got the material to do his calculations. “Those numbers, which included the relative distances of the repetitive elements in the DNA molecule, and the dimensions of what is called the monoclinic unit cell – which indicated that the molecule was in two matching parts, running in opposite directions – were decisive…

By chance, Franklin’s data chimed completely with what Crick had been working on for months: the type of monoclinic unit cell found in DNA was also present in the horse hemoglobin he had been studying for his PhD. This meant that DNA was in two parts or chains, each matching the other. Crick’s expertise explains why he quickly realized the significance of these facts, whereas it took Franklin months to get to the same point” [38].

Getting the missing pieces of the puzzle, J. Watson and F. Crick began to build a model based on the parameters obtained from the Franklin’s experiment.

They determined that the structure of DNA was a double-helix polymer, or a spiral of two DNA strands, each containing a long chain of monomer nucleotides, wound around each other [40]. “The novel feature of the structure is the manner in which the 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” [41]. According to their findings, DNA replicated itself by separating into individual strands, each of which became the template for a new double helix, “the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material” [41]. By March 1953, the mystery of life was revealed.

Watson and Crick DNA Model [42]

This discovery was probably the most outstanding discovery not only in the field of biology and medicine, but also in the history of science in general.

In April 1953, J. Watson, F. Crick, R. Franklin, and M. Wilkins published their articles in Nature. It was decided that the model would be published by J. Watson and F. Crick [41]. The articles of R. Franklin [43] and M. Wilkins [44] were published separately. In 1953, R. Franklin left King’s College, London, for Birkbeck College. She made important contributions to the X-ray crystallographic analysis of the structure of the tobacco mosaic virus. In 1958, she died. An inscription on her tombstone reads: “Her research and discoveries on viruses remain of lasting benefit to mankind” [45].

In 1962, F. Crick, J. Watson, and M. Wilkins were awarded the Nobel Prize in Physiology or
Medicine “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material” [46]. The Nobel Committee highly praised M. Wilkins’s contribution into the investigation of deoxyribonucleic acid of various biological origins by X-ray crystallographic techniques and Watson-Crick’s DNA model, emphasizing that this discovery would provide new possibilities to conquer disease and to gain a better knowledge of the interaction of heredity and environment and a greater understanding for the mechanisms of the origin of life.

Professor A. Engström, member of the Staff of Professors of the Royal Caroline Institute, in his Presentation Speech stated: “Dr. Francis Crick, Dr. James Watson, and Dr. Maurice Wilkins. Your discovery of the molecular structure of the deoxyribonucleic acid, the substance carrying the heredity, is of utmost importance for our understanding of one of the most vital biological processes. Practically all the scientific disciplines in the life sciences have felt the great impact of your discovery. The formulation of double helical structure of the deoxyribonucleic acid with the specific pairing of the organic bases, opens the most spectacular possibilities for the unravelling of the details of the control and transfer of genetic information” [47].

R. Franklin was neither awarded the Nobel Prize nor got enough credit for her dedicated scientific work. Firstly, her untimely death may have robbed her of the award, though no more than three recipients can share a Nobel Prize [48]. Secondly, R. Franklin became a victim of scientific disrespect that the report calls ‘gender harassment’ [49].

Whatever the DNA story is, it shows that all great scientific discoveries are not made from scratch. The immense number of people have contributed to the development of science and literally, every researcher stands on the shoulders of giants, while the idea itself is in the air.

The discovery of the structure of DNA became a cornerstone for the new scientific paradigm – biology acquired a molecular and biochemical basis. Deep research into DNA brought to the fore new technologies, which revealed the complex chemistry of protein synthesis and reproduction [29]. “In an influential presentation in 1957, Crick laid out the ‘central dogma of molecular biology’, which foretold the relationship between DNA, RNA, and proteins, and articulated the “sequence hypothesis”. A critical confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 in the form of the Meselson-Stahl experiment. Work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, and Har Gobind Khurana and others deciphered the genetic code not long afterward (1966). These findings represent the birth of molecular biology” [6].

Life paths of the great DNA pioneers moved off in different directions. M. Wilkins continued research as a leader of a team that performed a range of experiments to establish the helical model as valid among different biological species, as well as in living systems, and to approve the universality of the double helix structure. He applied X-ray techniques to the structural determination of nerve cell membranes and of ribonucleic acid [50]. He became Deputy Director of the MRC Biophysics Unit at King’s College, London, in 1955, and succeeded Randall as director of the unit from 1970 to 1972 [51]. In 1959, M. Wilkins was elected a Fellow of the Royal Society. In 1960, he was presented with the American Public Health Association’s Albert Lasker Award. In 1962, he became a Commander of the Order of the British Empire. In 1964, he was elected a European Molecular Biology Organization Member. In 2003, his book “The Third Man of the Double Helix: The Autobiography of Maurice Wilkins” was launched [52]. He died in 2004.

J. Watson’s subsequent career eventually took him to the Biology Department at Harvard University, where he was focused on RNA and its role in the transfer of genetic information. In 1968, he took over the directorship of the Cold Spring Harbor Laboratory of Quantitative Biology on Long Island, New York. From 1988 to 1992 he headed the National Center for Human Genome Research at the National Institutes of Health. Afterward, he returned to the Cold Spring Harbor Laboratory. J. Watson retired in 2007.

To raise money, DNA pioneer sold his Nobel Prize medal at Christie’s in 2014. He became the first living Nobel Prize recipient to sell his medal. J. Watson intended to donate some money to Cold Spring and to University College Cork in Ireland [53]. A Russian billionaire A. Usmanov bought the medal and returned it to J. Watson commenting on the situation: “In my opinion, a situation in which an outstanding scientist has to sell a medal recognizing his achievements is unacceptable… Dr. Watson’s work contributed to cancer research, the illness
from which my father died. It is important for me that the money that I spent on this medal will go to supporting scientific research, and the medal will stay with the person who deserved it” [54].

J. Watson has won numerous awards, including Albert Lasker Award for Basic Medical Research (1960), Eli Lilly Award in Biological Chemistry (1960), Presidential Medal of Freedom (1977), European Molecular Biology Organization Membership (1985), Golden Plate Award of the American Academy of Achievements (1986), Copley Medal of the Royal Society (1993), Lomonosov Gold Medal (1994), National Medal of Science (1997), Liberty Medal (2000), Benjamin Franklin Medal for Distinguished Achievement in the Sciences (2001), Honorary Member of Royal Irish Academy (2005), Othmer Gold Medal (2005), CSHL Double Helix Medal Honoree (2008), etc. In 2003, J. Watson became one of 22 Nobel Prize winners to sign the Humanist Manifesto [55].

F. Crick continued working at the Cavendish Laboratory. In 1958, he substantiated his Sequence Hypothesis in “On Protein Synthesis” [56]. He proposed that any specific sequence of A-T-C-G bases in DNA is a code for building a specific amino acid sequence in a protein. He predicted the discovery of an adaptor that carries information from DNA to protein – transfer RNA [39].

In 1960, F. Crick accepted an honorary fellowship at Churchill College, Cambridge. During his tenure, he made fundamental contributions to unlocking the genetic code. Together with S. Brenner, they demonstrated that each group of three adjacent bases on a single DNA strand codes for one specific amino acid [57]. After many years at Cambridge, F. Crick joined the Salk Institute for Biological Studies in California, where he conducted research on the neurological basis of consciousness – the other great mystery that had intrigued him along with the mystery of life. He died aged 88 in 2004.

F. Crick received many medals and honors, including The Royal Society Fellowship (1959), as well as the International Academy of Humanism and CSICOP Fellowship, European Molecular Biology Organization Membership (1964), the Royal and Copley Medals of the Royal Society (1972, 1975), the Order of Merit (1991), the Benjamin Franklin Medal for Distinguished Achievement in the Sciences of the American Philosophical Society (2001). He was the author of “Of Molecules and Men” [58], “Life Itself: Its Origin and Nature” [59], “What Mad Pursuit: A Personal View of Scientific Discovery” [60], “The Astonishing Hypothesis: Scientific Search for the Soul” [61].

Nowadays, our understanding of biology and medicine is based on the knowledge of the structure of DNA as a carrier of genetic information. This knowledge provides us with the opportunity to intervene efficiently in the processes and phenomena of life at all its levels [62]. However, Knowledge is a double-edged sword. Today more than ever, the responsibility and ethics of scientists, politicians, and world leaders, whose hands this Knowledge is in will come to the forefront. The Future of humanity depends on whether this Knowledge of the Book of Life is used for good or evil.
не отримала належного визнання за цю свою наукову роботу. На відміну від неї, Френсіс Крік, Джеймс Уотсон та Моріс Вілкінс були удостоєні Нобелівської премії з фізіології або медицини 1962 р. «за відкриття щодо молекулярної структури нуклеїнових кислот та їх значення для передачі інформації в живому матеріалі». Але якою б не була історія ДНК, вона свідчить про те, що всі велики наукові відкриття виникають не на порожньому місці: велика кількість людей сприяє розвитку науки, і буквально кожен дослідник стойть на плечах «гігантів»-попередників, а сама ідея «витає в повітрі». Що ж до розшифровки структури ДНК в 1953 р., можна стверджувати, що вона стала одним з поворотних моментів в історії біології. Це фундаментальне відкриття змінило та надало нашому життю багато нових аспектів. Воно поклала початок бурхливому розвитку генетики та молекулярної біології, який триває і в наші дні, а подвійна спіраль ДНК стала символом науки про життя.

Ключові слова: ДНК, подвійна спіраль ДНК, Джеймс Уотсон, Френсіс Крік, Роза-лінд Франклін, Моріс Вілкінс, Нобелівська премія з фізіології або медицини 1962 року.

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