Francis Crick in Molecular Biology

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Keywords: Crick, DNA, Protein, Genetic Codes, Molecular Biology

Abstract: This article is a tribute to Francis crick, a biophysicist who passed away on July 28, 2004. Francis crick, James Watson and Maurice Wilkins were jointly awarded the 1962 Nobel Prize for physiology or medicine for discovering the molecular structure of nucleic acids and its significance for information transfer in living material. It is pointed out that the diverse background and unique sensitivity of crick to science enabled him to have great insights into frontier research. He had a special capacity for prudent and logical thinking, which contributed so much to the development of molecular biology. Based on Francis crick's academic achievements in molecular biology and by virtue of internal history approaches such as concept analysis and literature research, this paper is aimed at revealing the historical contributions of crick in a condensed way and to commemorate his work.

1. Introduction

Francis crick (figure 1) was born on June 8, 1916 as an English citizen, and he left the world, aged 88. With lifelong devotion to scientific research, crick is credited as one of the central figures in the molecular revolution that swept through biology in the latter half of the twentieth century [1]. Keen on seeking after and tackling the profound problems, he developed a passion for biology although crick did research in physics at the beginning of his scientific life [2,3]. Having with James Watson discovered the structure of deoxyribonucleic acid [4], in 1962 crick won him a share in the Nobel Prize in physiology or medicine. This discovery changed much of 20th century science.

Fig.1: Crick in Contemplation

Note: This Watercolor is the Work of Crick's Wife (Odile Crick), and Intended to Show the Contemplative Crick; the Picture Was Taken Thanks to Crick's Daughter (Gabrielle Crick) in Her London Home on June 28, 2015.

  DOI: 10.25236/acete.2019.101

Following the careful investigation of DNA, he continued to play a central role in the elucidation of the genetic codes and the mechanism of protein synthesis. So much achieved, he became a "molecular evangelist". The later years of crick's life were spent in California, where he plunged into the complex world of neuroscience he earlier selected as the second significant issue to touch on.

There have been many excellent works that concentrated on crick's scientific journey from historical perspective so far, such as "the eighth day of creation: makers of the revolution in biology"[5], "the path to the double helix: the discovery of DNA"[6], "Francis crick: hunter of life's secrets"[7], "Francis crick: discoverer of the genetic code "[8], and so on. More intriguingly, his own memoir "what mad pursuit" absolutely reflects his insights into science and even overview of what he was doing [9]. The paper was aimed to reveal the historical contributions of crick in the field of molecular biology [10] in a condensed way for commemorating his great work.

2. Protein Structure

Before crick fixed his attention on DNA, he had been willing to research into protein structure. He learned a lot both by himself and from his supervisor, max perutz, learning the skill of using diffraction from single molecules and then arranging them in a regular crystal lattice, forsaking the more conventional path of starting off with them in a lattice. As to α helix spot, crick not only with bill Cochran and other two crystallographers, worked out the general nature of the fourier transform of a set of atoms arranged on a regular helix in the Cavendish lab but also, with bill, showed that it fit rather well the x-ray pattern of synthetic polypeptides. More encouragingly, he and linus pauling independently hit on the correct explanation, "because of their non-integer screw, α helices do not pack easily side by side. They pack best when there is a small angle between them, and, if they are deformed slightly, this leads to a coiled coil…This additional coiling threw the 5.4å off-meridianal spot onto the meridian at 5.1 å. [9]"

The approach crick applied to dealing with protein structure proved to be incredibly effective afterwards. He predicted that only the "isomorphous replacement" method could give people the detailed structure of a protein. Historically speaking, this approach solved the phase problem in x-ray crystallography. It was confirmed by crick that this method had the best prospect of success and the work he had been doing would enable his opinion of prediction to be fulfilled quickly [9]. "replacement" meant that he had replaced a light atom or molecule, such as water, with a heavy atom, such as mercury, which diffracts the x rays more strongly. "isomorphous" implied that the two protein crystals-one with the mercury and one without-should have the same form(for the unit cell).he was aware that it was not enough that if people wanted to reconstruct the three-dimensional picture of electron density to help locate the many thousands of atoms in the crystal. X-ray diffraction normally gave only half the information he needed.

How to acquire the whole information at that time?Crick went through each method in turn, including the patterson, and tried to demonstrate all but one was quite hopeless. That promising means was "isomorphous replacement" mentioned above. "suppose a very atom in the crystal, such as, mercury, can be added to the crystal at the same spot on every one of the protein molecules it contains. Suppose this does not disturb the packing together of the protein molecules but only displaces an odd water molecule or two. We can then obtain two different x-ray patterns, one without the mercury there, and the one with it. By studying the differences between the two patterns we can, with luck, locate where the mercury atoms lie in the crystal. Having found these positions, we can obtain some of the missing information by seeing, for each x-ray spot, whether the mercury has made that spot weaker or stronger." [9]

Eventually crick finished his ph.d. Thesis: "x-ray diffraction: polypeptides and proteins" and received his degree in 1954. in 1955, he worked with alexander rich, dealing with the structure for collagen. The collaboration between them was a big part in crick's scientific life. Their findings exactly involved the discovery of the basic structure of collagen, the cartilage and other tissues. Although collagen is everywhere, perhaps because it is so ordinary, it is not as famous as DNA [9].

3. DNA Structure

It is well known that the nobel prize of physiology or medicine in 1962 was awarded jointly to crick, watson and maurice wilkins “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material”. With the aspect to the cooperation between crick and watson on the way to figure out the material structure of DNA, they both provided the key steps [11,12]. Watson’s merit was to define the exact nature of two base pairs (a with t,g with c).crick gave him the very good comments at this point “in a sense jim’s discovery was luck, …,the important point is that jim was looking for the significant and immediately recognized the significance of the correct pairs when it hit upon by chance. [9]”

Crick combined physics methods with the construction of DNA model. Crick was convinced that model building plays a vital role in coping with DNA. The suggestion from him was that it should be phosphates on the outside rather than on the inside of DNA structure which watson firmly insisted on for a period. The argument about the inside or outside of the position of phosphates was timely reminder to watson and had the important effect of directing our attention to the bases leading to the correct model. Furthermore, relatively easily crick could deduce the anti-parallel direction of the two chains from x-ray photographs with c_2 space group structure rosalind franklin had provided. He could realize an implication of this symmetry that franklin had overlooked and deepen the understanding of c_2. There must be a two-fold rotation axis lying at right angles to the axis of the chain. This condition was able to be satisfied only by a chain with an even number of strands lying in an anti-parallel array.

When these two features [13], base pairing and anti-parallel, were taken into consideration, a model of the DNA chain was built. Certainly their work was based on pauling’s example, erwin chargaff’s rules, the outstanding and effective experiments of wilkins and franklin and some efficient discussions with each other. It successfully formed a comprehensive research outcome, DNA double helix combining biology, physics, chemistry and mathematics.

One more important point to emphasize is that when watson and crick decided to publish the productive results about DNA structure, crick insisted that they should have priority by use of the short sentence :”it has not escaped our notice that the specific paring we have postulated immediately suggests a possible copying mechanism for the genetic material.” Crick made clear the genetic meaning of double helix. Also later on the DNA structure was being doubted by other people with different models until in the 1980’s the double helix was confirmed really[14].

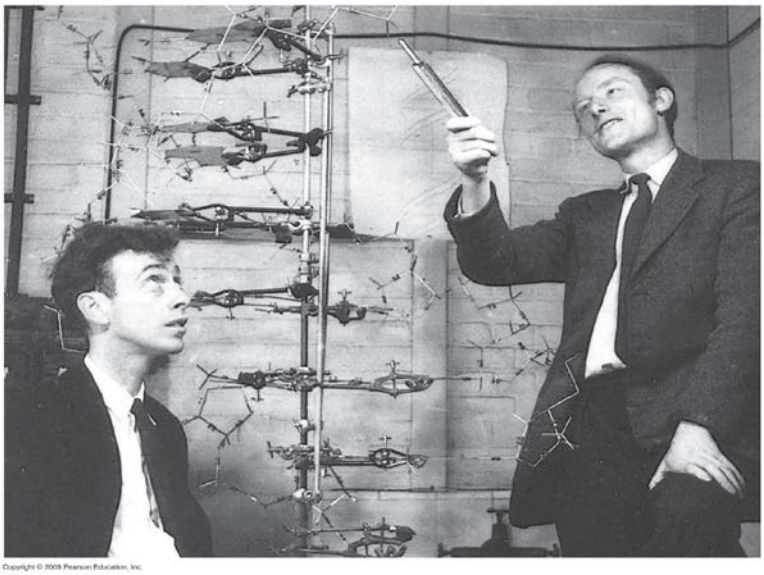

Fig.2: Francis Crick and James Watson in DNA Research (Soraya de Chadarevian, 2003)

Note: This Picture Was Taken Originally by Antony Barrington Brown.

In both science and history community, people do value the strong team work between crick and watson who definitely set a perfect example during the process(see figure2). It is indicative of the

advantages of intelligent cooperation until today. As crick said: “our other advantage was that we had evolved unstated but fruitful methods of collaboration…if either of us suggested a new idea the other, while taking it seriously, would attempt to demolish it in a candid but non-hostile manner. This turned out to be quite crucial. “

4. Central Dogma

Crick has an inspiring track record of grasping the key problems; as he put it: “proteins are a family subtle and versatile molecules. As soon as i learned about them i realized that one of the key problems was to explain how they were synthesized.” And “thus the general plan of living things seemed almost obvious. Each gene determines a particular protein. Some of these proteins are used to form structures or to carry signals, while many of them are the catalysts that decide what chemical reactions should and should not take place in each cell. Almost every cell in our bodies has a complete set of genes within it, and this chemical program directs how each cell metabolizes, grows and interacts with its neighbors. Armed with all this (to me) new knowledge, it did not take much to recognize the key questions. What are genes made of?How are they copied exactly?And how do they control, or at least influence, the synthesis of proteins?” [9]

In 1958 the paper, “on protein synthesis”, was powerful symbol of his early research on the frame of molecular biology. He pointed out, “once ‘information’ has passed into protein it cannot get out again.” Also the clear definition for “information” was given in his paper[15]. Information at this point referred to the accurate sequences, “information means here the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein.” At that time, central dogma implied that the transfer of genetic information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. The whole process includes three stages, replication (DNA→DNA), transcription (DNA→mrna) and translation (mrna →protein). From 1958 to 1970, central dogma experienced completing itself twice, which was the source of confusion and controversy among many scholars and researchers. Therefore, he supplemented his opinion about the central dogma “central dogma of molecular biology” in 1970, redefining the contents and meaning of central dogma objectively [16].

Crick clarified his stance about “the central dogma enunciated by himself in 1958 and the keystone that molecular biology ever since, is likely to prove a considerable over-simplification.”, saying that “perhaps the so-called repetitive DNA is produced by an rna→DNA transfer. Any of these would be of the greatest interest, but they could be accommodated into our thinking without undue strain. On the other hand, the discovery of just one type of present cell which could carry out any of the three unknown transfers would shake the whole intellectual basis of molecular biology. And it is for this reason that the central dogma is as important today as it was proposed.” Crick made a detailed deduction in relation to information transfers that involve “general transfers, special transfers and unknown transfers” (table 1). These three kinds of transfers explicitly cover how the information flows between DNA and rna and protein in the central dogma.

Table 1 the Three Classes of Information Transfers

General	Special	Unknown
DNA → DNA	Rna → DNA	Protein → DNA
DNA → Rna	Rna → Rna	Protein → Rna
Rna → Protein	DNA → protein	protein → protein

When he faced the trouble, “the use of dogma caused almost more trouble than it was worth. Many years later Jacques Monod pointed out to me that I did not appear to understand the correct use of the word dogma, which is a belief that cannot be doubted.” Crick explained, “I called this idea the central dogma, for two reasons, I suspect. I had already used the obvious word hypothesis in the sequence hypothesis, and in addition I wanted to suggest that this new assumption was more central and more powerful. ... I did apprehend this in a vague sort of way but since I thought that all

religious beliefs were without foundation, I used the word the way I myself thought about it, not as most of the world does, and simply applied it to a grand hypothesis that, however plausible, had little direct experimental support." Today, the central dogma provides the theoretical frame for molecular biology, and stands the test of history and practice, and deserves a profound biology dogma [17].

Philosophers have some comments like "Crick delineated flow of matter, flow of energy and flow of information in the mechanism of protein synthesis and clearly focused on information flow. What mattered to molecular biologists such as Watson and Crick was tracing information flow, that is, the preservation of linear order and pattern from one stage of the mechanism to the next. [18]„ Historian Robert Olby has ever said" in 1957, Crick defined biological 'information' as the sequence of the bases in the nucleic acids and of the amino acids in proteins, and proposed the now famous 'central dogma' according to which information so defined flows between the nucleic acids and proteins only in one direction - from the former to the latter[17]. Just four years later, Marshall Nirenberg and Heinrich Matthaei successfully synthesized a polypeptide constituted of only one kind of amino acid (phenylalanine) using a RNA composed only of one kind of base (uracil). They concluded that "one or more [of these RNA bases] appear to be the code for phenylalanine. [19]„

5. Genetic Codes

From the collection of Medical National Library, USA provided by Wellcome library [20], more than half of the original papers written by Crick was directly relevant to Genetic Codes. The more enthusiasm about the issue how protein would be synthesized definitely led to the research on Genetic Codes [21,22], a critical link between DNA and protein. The work of Crick in Genetic Codes is a clear demonstration of the theoretical exploring, of creative guesswork and successful integration.

All he focused on involves two-level research that was indication of his efforts in genetic codes. The first level includes his fundamentals such as coding problem, protein synthesis and triplet, while the second is made of the syntheses with the properties of genetic code, wobble hypothesis, stop codons, the construction of the standard code table and the origin and evolution of codes [23,24].

Fig.3: Francis Crick and His Second Collaborator Sydney Brenner

(From wellcome online archives)

Based on the structure of DNA, physicist George Gamow is the first person who proposed the numeric theory of code problems [25], then Crick discussed the code-words with Watson. In 1954, he

met another close collaborator, Sydney Brenner(see Figure3), and dedicated his time to the study of genetic codes for 15 years. In 1961, Crick, Brenner and Leslie Barnett published the paper, in which it was the first time to prove every code is triplet by genetic methods [26] and put the phrase “genetic code” in use. That was substantial progress. His thoughts in code problems provided the reliable support in theory and constructive guidance in skills for cracking the total 64 codes in laboratories [27].

Very soon three groups in USA, Nirenberg, Har Khorana and Severo Ochoa [28] made great efforts and succeeded in decoding the codes respectively. In June, 1966, the symposium at Cold Spring Harbor Laboratory is mainly about the genetic codes. Crick became the focus of this conference. He formulated the past, the present and the future both in theory and in experiment [28] . It is Crick who, from start to finish, played a leading role in genetic codes. Even compared to beautiful and charming DNA molecule, he was extremely proud of the work on genetic codes with his own remark “The genetic code was not revealed all in one go, but it did not lack for impact once it had been pieced together. I doubt if it made all that much difference that it was Columbus who discovered America. [9]”

After the relationship between 64 genetic codes and 20 amino acids was clear, Nirenberg, Khorana and Robert Holley were jointly awarded the Nobel Prize in 1968[19], based on their dedication to genetic code. It is in the same year that Crick put the finishing touches on the cipher chart lexicon that has been recognized until today. Although Crick did not get the special prize, he really deserved the top reward.

The progress in the genetic codes [29,30] indicates that it is transparently true that DNA was considered as a genetic material. People would have the better and deeper understanding of genetic mechanism regarding the genetic codes [31,32,33] as the core of molecular biology. Currently, the theoretical research in genetic codes still centers on the code table [34]. More interestingly, the deeper research people have been making is to modify genetic codes [35], expand genetic codes and synthesize new proteins [36,37] using this molecular framework.

6. Conclusion

Crick’s interest in science continually transferred from one field to another, beginning with physics, then biophysics and then neuroscience. His scientific thinking was enhanced by his solid foundation in physics prior to entering biology field. The significant background and sensitivity to science enabled him to have great insights into the frontier line research and prudent logical thinking, and he even became a brilliant influencer of big science [38]. He emphasized research objects themselves could generate results based on the evidence. With regard to the big choice in his career, Crick first inclined to be engaged in biophysics willingly, and then never stopped pursuing the intrinsic essence of substance itself. Through his scientific journey, it was not just about physics elements, but also biology targets, and even a combination of both with his perseverance and intelligence. As Eagleman wrote in Obituary for Crick, it read “By the 1960s, thanks largely to the work of Francis Crick and his circle of friends, the molecular basis of inheritance was worked out…….Francis went on to blaze trails in molecular biology, laying the groundwork for everything that would happen in that field over the next half-century” [39]. Carl Woese held “there was Francis Crick, the most charismatic figure in 20th century biology; however, I learned more by nipping at his heels than by following his lead” [40].

In the history of science, the exposure of the DNA structure opened up a new chapter. The application of X-diffraction technology to biology molecules was interdisciplinary and allowed biophysics to developing continuously. Meanwhile, there were other emerging cross-disciplinary interactions in biology, biochemistry and bioinformatics. At present, cross-disciplinary is very dynamic, and thought-exchanging across the discipline is becoming the most driving force for the development of science and technology [41]. In the light of interdisciplinary thinking, Crick had his own standpoint, “Classical genetics is, after all, a black-box subject. The important thing was to combine it with biochemistry.” In nature hybrid species are usually sterile, but in science the reverse is often true. Hybrid subjects are often astonishingly fertile, whereas if a scientific discipline

remains too pure it usually wilts. [9]" Eventually, his whole scientific lifestyle indicated that the connection between the concepts of physics and biology objects led him to tremendous success in his research.

In 2016, Francis Crick institute, supported by the Medical Research Council, Cancer Research UK, the Wellcome Trust, and University College London, King's College London and Imperial College London was opened [42]. The institute puts emphasis on research training and early independence of gifted scientists in a multidisciplinary environment,which provides unique opportunities for UK medical science, including clinical and translational research. People trust the institute and research itself will be the expansion of Crick's spirit.

Acknowledgment

Funded by National Social Science Foundation" Research on the historical contribution of population scientists in the field of genetic code" (XSS001)

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