Commentary

The death of Francis Crick: the end of a golden age in biology

Born in 1916, Francis Harry Compton Crick studied physics at University College, London, where he devoted his first scientific efforts to studying the viscosity of water at high temperatures. During the war, he participated in the development of 'noncontact' magnetic and acoustic mines. Like many other young physicists, he switched to biology after the Second World War, bored by the now dull studies pursued in physics, and attracted by the new frontier of knowledge that was biology, a discipline where the concepts and techniques of physics were desperately needed. He spent two years at the Strangeways Laboratory in Cambridge studying the physical properties of cytoplasm, and joined the Medical Research Unit at Cavendish laboratory headed by Max Perutz to study protein structure by X-ray diffraction studies.

The decision he made with Jim Watson to focus on the structure of DNA, and the huge impact this structure had on the development of molecular biology, are well known. Francis Crick received with Jim Watson and Maurice Wilkins the Nobel Prize in Physiology or Medicine in 1962 for this discovery. To consider that determining the structure of DNA was the right way to understand the power of genes was a brilliant piece of foresight at a time when the results of Oswald Avery showing that genes were made of DNA were largely ignored. Watson was the leader in the construction of the model, adopting a strategy previously used by Linus Pauling for the study of proteins. Given his excellent knowledge of crystallography and X-ray diffraction, Francis Crick had all the skills required to provide the firm materials for the elaboration of the model and to relate it to the X-ray diffraction pattern obtained by Rosalind Franklin. Francis Crick made major additional contributions to crystallography by characterizing the diffraction properties of helices, as well as by determining the structure of viruses and playing a role in the characterisation of collagen structure. Paradoxically, his competences led him to be somewhat sceptical about the possibilities of X-ray diffraction, an attitude not appreciated by his colleagues . . . before 1953.

Between 1953 and 1961, the major contribution of Francis Crick to molecular biology was the constant support he provided to the hypothesis of the genetic code, introduced by the physicist George Gamow immediately after the publication of the Watson-Crick model. Based on the belief that a nucleic acid can interact only with another nucleic acid, he proposed in 1954 the adaptor hypothesis. According to it, a short oligonucleotide known as an adaptor served as a link between the amino acid and the RNA involved in protein synthesis. This hypothesis was confirmed four years later by Mahlon Hoagland in Paul Zamecnik's lab. Crick's most influential article was the transcription of a lecture given in 1957 entitled 'On protein synthesis'. In this article, he clarified the relations between DNA, RNA and proteins. He suggested that the final conformation of a protein was simply a function of its amino acid sequence. He officially proposed the sequence hypothesis – that the sequence of nucleotides is the information determining the sequence of amino acids in the proteins, another way to formulate the conception of a genetic code. He also introduced the central dogma, the claim that genetic information can flow from nucleic acids to proteins, but not in the reverse direction: a last blow to the Lamarckian theory at the molecular level.

Francis Crick was not at the origin of the deciphering of the genetic code. This was done by Marshall Nirenberg and Heinrich Matthaei in 1961, using an *in vitro* protein biosynthesis assay, the kind of biochemical method that Francis Crick was not fond of. However, he did initiate two important studies that contributed to the characterization of the genetic code: the demonstration by Vernon Ingram in 1957 that the genetic mutation at the origin of sickle-cell anemia consisted in the precise replacement of a given amino acid by another – strongly supporting the idea that genes directly controlled the sequence of amino acids in proteins–, and the insertional mutagenesis work done by Sydney Brenner in the B cistron of the rII region of the bacteriophage T4, which elegantly demonstrated that the codon, the unit of information in the nucleic acids, consisted of a triplet of nucleotides. He proposed the wobble pairing hypothesis to describe the interactions between tRNA and mRNA and to explain the degeneracy of the genetic code. He also played a determining role in the identification of an RNA intermediate between DNA and proteins, the messenger RNA. When reverse transcriptase – the enzyme that copies RNA into DNA was discovered in 1970, the notion of central dogma was harshly criticized. The choice of the word dogma was unfortunate. However, despite this weakness, the 1957 lecture was an essential step towards the clarification of the relations between the three informational macromolecules present in organisms. The hypothesis that information could not be transferred from RNA to DNA was not included in the 1957 lecture; it was later introduced by Jim Watson.

After this revolutionary period when the paradigm of molecular biology was built, Francis Crick made many further important contributions that constituted major landmarks for biologists. With Leslie Orgel, he tried to elaborate a scenario for the origin of life and of the genetic code. He suggested that RNA was the macromolecule that played the major role in the first steps of life. The discovery of the catalytic activity of RNA at the end of the 1970s and the hypothesis of the RNA world were tributes to the anticipations of Francis Crick. He made the concept of 'diffusion gradients' in embryonic systems respectable by showing that diffusion of a small molecule could set up appropriate gradients within a reasonable time and over an appropriate tissue size – for instance, in the tissues of an insect. In addition, he supported the theories of García-Bellido, Peter Lawrence and others in the 1970s concerning the role of genes in development, leading to the developmental gene concept. The selfish DNA model elaborated with Leslie Orgel provided an explanation for the abundance of non-coding DNA with no apparent function in the genome. In 1970, Crick proposed an original model of gene regulation in eukaryotes, giving single-stranded DNA a major role. This model was not however confirmed by subsequent studies of gene regulation. In addition, he was a very keen observer of the progressive transformations of molecular biology as it extended to the study of higher organisms, and he commented with great perspicacity on the discovery of odd phenomena such as DNA supercoiling and RNA splicing.

He joined the Salk Institute in 1976, where he started his final study on the neural correlates of consciousness, or to use the more striking subtitle of his last book, 'the scientific search for the soul'. It is far too early to appreciate his contributions in this field. The main result of his activity was probably to make scientific studies on consciousness respectable and even fashionable. His interest in consciousness at the end of his scientific career was obviously not an accident. His underlying motivation when he entered the field of biology was to show that living systems could be explained by chemistry and physics, in agreement with his own view of the world as an atheist. According to him, the discovery of the double helix structure of DNA was the solution to the riddle of life. The last frontier of knowledge, the domain where mystery and religion could still hide, was consciousness. Francis Crick did not have the time to explain the chemical and physical mechanisms at the origin of consciousness as he did before for those involved in the transmission of genetic information. It is quite remarkable that, before him, Max Delbrück – leader of the bacteriophage group and considered for that reason as one of the fathers of molecular biology – pursued the same journey, from genes to consciousness: in his case, to find the physical laws specific to organisms, that he looked for in the study of bacteriophage reproduction, but in vain.

Francis Crick, a theorist rather than an experimentalist, found a very favourable niche for his major contributions between 1950 and 1960, during the progressive shaping of molecular biology. He never immediately rebutted a new idea. His theoretical models were not quantitative, and were uniquely designed to stimulate experimentation: all his life Francis Crick collaborated very closely with experimentalists, finding that such collaborations were the best way of being efficient. His work is emblematic of a very specific phase in the development of biological sciences, a time when it was possible to privilege theories and not to abandon them due to a few contradictory facts. His late contributions were less influential, as biology had become experiment-driven once again. Francis Crick's achievements will remain the best icon of this golden age of biology, when a new view of the most fundamental mechanisms of life was progressively established.

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