Commentary

F H C Crick (1916–2004)

Francis Crick, who died recently at the age of 88 in San Diego, occupies a very special place in science. In 1953 Watson and Crick described the double-helical structure of DNA. This discovery has been variously described as the most revolutionary of all contributions to biology; the greatest since Darwin's theory of evolution and Mendel's principles of heredity; together with relativity, the most important discovery of the 20th century. None of this is an exaggeration. The history of biology does not provide many instances of grand, unifying generalizations. The theory of evolution, Mendel's laws and the genetic code stand out as shining examples. One might like to add bio-electricity (Galvani and Volta) and the neuron theory (Ramon y Cajal) but it is hard to think of more such cases.

The Watson-Crick hypothesis first appeared as a short statement at the end of an otherwise parsimonious paper on the molecular structure of nucleic acids in the *Nature* issue of 25th April 1953 ". . . it has not escaped our attention that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material". The anecdote goes that two months earlier Crick had walked into the Cambridge pub, The Eagle, and proclaimed publicly that he and Watson had discovered the secret of life.

In a paper published a few weeks later Watson and Crick stated more explicitly the implications of their work. The structure of DNA they had proposed solved three outstanding problems concerning genes: the nature of genetic specificity (we now call it genetic information), the basis of self-duplication ('secret of life') and the molecular nature of genetic mutation (the basis of evolution). All three were long-standing problems that had occupied scientists, particularly the chemically-minded geneticists, in the nineteen thirties and forties. That genes are made of DNA was discovered by Avery in 1945 but the import of Avery's work had not been registered by mainstream biology. Leading geneticists were still thinking of the gene as a protein molecule or some form of a protein-nucleic acid complex. Crick and Watson clearly showed how, in fact, a gene could work.

When first formulated, Crick's hypotheses about colinearity of DNA and protein, semi-conservative replication of DNA, nature of mutation and mechanisms of translation were conjectures. In the years between 1953 and the sixties, molecular biology was largely occupied with working out the consequences of Crick's ideas. Crick himself remained at the center of the movement. "No one created molecular biology" said Jacques Monod "but Francis Crick dominates the whole field intellectually because he knows and understands the most". After 1953, Crick's principal interest was the genetic code and the mechanism of protein synthesis. He now closely collaborated with Sydney Brenner, the two sharing an office in the Cavendish Laboratory. Crick and Brenner understood that the full solution of the problem must come from biochemical experiments. But, by a series of brilliant theoretical arguments and simple genetic experiments, they showed that the code was degenerate, non-overlapping and read in triplets from a fixed starting point. They had discerned the general features of the code before it was actually deciphered. Marshall Nirenberg and Matthaei developed an *in vitro* protein synthesis reaction, which needed a polynucleotide template. The sequence of the polypeptide was specified by the sequence in template RNA. The entire code was solved by using this reaction. To begin with, the synthetic polynucleotides were first of random sequences made with polynucleotide phosphorylase in Ochoa's laboratory. Later, templates of definite sequences were used by Khorana.

It was known that proteins are synthesized in the cytoplasm, not in the nucleus, and that RNA was somehow involved. But the role of different species of RNA was not understood. The cosmologist George Gamow was instrumental in starting a group called the RNA tie club to deal with problems emanating from the genetic code. Among the members of the club apart from Gamow, Crick, Brenner and Watson were Alexander Rich, Martynas Ycas, Leslie Orgel and Albert Szent-Györgyi. Members of

the club exchanged ideas and papers. Crick's paper on the commaless code, which appeared in the *Proceedings of the National Academy of Sciences, USA* in 1957, was first circulated to the RNA tie club. The Editor of the *Proceedings of the National Academy of Sciences* returned a paper by Gamow because it had, as a co-author, the non-existent Mr Tompkins. In a manuscript circulated in the mid-fifties Crick suggested that RNA acts as an adaptor that enables amino acids to associate with nucleic acids. Soon afterwards, Hoagland and Zamecnik discovered transfer RNA. Crick proposed the wobble hypothesis in which tRNA could bind in two different ways giving rise to ambiguity in coding.

Crick's interests were broad. Nothing important in biology escaped his roving eye. He generated seminal ideas, often circulated as unpublished manuscripts. The novel ideas that can be ascribed to Crick cover an array of subjects such as intragenic complementation, the nature of suppressor mutations, segmentation and complementation in development and origin of life on earth. Crick was a theorist who delighted in focussing the light of his highly original and sharp mind on important unsolved problems. But his theories were not overly quantitative or computational. The main thing in any theory, Crick emphasised, are postulates, not algebra. Crick insisted on setting out one's postulates with clarity so that they could be tested.

In 1970, Crick classified the unsolved problem of biology into three categories, those that were likely to be solved before the end of the 20th century, those that were difficult but would be solved in a few decades and problems that were so difficult that their solutions could not be foreseen. He placed the issues connected with awareness or consciousness in the last category. Crick himself turned to neuroscience in the seventies. He moved to the Salk Institute where he collaborated with Graeme Mitchison and Christof Koch over many years. Crick's ideas on the nature of consciousness, or awareness as he preferred to call it, are set forth in his book "*The Astonishing Hypothesis*", and the recent book by Koch, *The Quest for Consciousness*. *The Astonishing Hypothesis* is an important work not for any major new discoveries that it describes, but as a forceful presentation of Crick's approach to the problem and for his wit and elegance. The main idea that Crick advocates is that the explanations of apparently mysterious properties of the animal brain are to be sought in the activities of its neurons, in chemistry and neurobiology, rather than in something God-given. Thought, emotion, character, free will, in short the human 'soul', are to be understood in terms of brain activity. The idea might seem astonishing to many but it is not unfamiliar to the followers of Charles Darwin. Crick's book is not so much a review of new findings as a program of research to attract ambitious young scientists to neuroscience. At the end he gives a reading list of some sixty books that an entrant to this area might like to read. Accompanying the list are Crick's own delightfully candid comments. Here are two examples:

Popper Karl R and John C Eccles, "*The Self and Its Brain*", Springer Verlag 1985.

"Popper is a philosopher. Eccles is a neuroscientist. The book is in three parts, the first part by Popper, the second by Eccles and the third a dialogue between the two. Both of them are dualists – they believe in the ghost in the machine. I myself have little sympathy with either of their points of view. They would probably say the same of mine".

Penrose Roger, "*The Emperor's New Mind*", Oxford University Press 1989.

"Penrose is a distinguished mathematician and theoretical physicist. He believes that the brain can execute processes that no possible Turing type computer could carry out. He considers physics incomplete because there is yet no theory of quantum gravity. Penrose thinks that an adequate theory of quantum gravity might explain the mystery of consciousness, but he is characteristically vague as to how it might do so. At bottom his argument is that quantum gravity is mysterious and wouldn't it be wonderful if one explained the other. Much of the book deals with such topics as Turing Machines, Gödel's theorem, quantum theory and the arrow of time, all explained with great thoroughness and clarity. There is a little about some of the properties of the brain, but practically nothing about psychology. Penrose is a Platonist, a point of view not to everybody's taste. It will be remarkable if his main ideas turn out to be true".

Crick was gifted with a striking personality. Tall, slender and very English, he combined a fierce intellect with great charm and a ringing laughter. His humor was sharp but not malicious. On one occasion I checked with him on his willingness to be elected to the Indian Academy of Sciences. When I

said the Academy looked for an Indian connection in its Foreign Fellows, Crick remarked "I inherited some shares in a tannery in Madras from my uncle. Unfortunately I have sold them." Once I asked him what made him change to brain research. "You should know", he replied, "You have done something of the sort yourself. Perhaps we didn't realize DNA would be so easy to sequence".

Crick took his success lightly. "We were lucky with DNA." he writes, "Like America it was waiting to be discovered" . . . "By blundering about we stumbled upon gold but Jim and I must at least be credited with the fact that we were looking for gold". At the same time he was kind and considerate. Watson has said "I will always remember Francis for his focussed intelligence and for the many ways he showed me kindness and developed my confidence . . . . Francis was a person with whom I could most easily talk about ideas". I can do no better than to refer the reader to a moving reminiscence of Crick by Graeme Mitchison that has appeared in the *Journal of Genetics* of August 2004. To an entire generation of young scientists who grew in molecular biology in its golden decade, 1953–1963, Crick was an inspiring role model. The mark that Francis Crick made on biology is indelible. One hopes that the style and attitudes that he brought to research will also endure.

OBAID SIDDIQI
National Centre for Biological Sciences,
GKVK Campus,
Bangalore 560 065, India
(Email, osiddiqi@ncbs.res.in)

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