Current Biology Vol 14 No 16
R642

Obituary

Francis Crick 1916–2004

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"*At first I could see nothing, the hot air escaping from the chamber causing the candle flame to flicker, but presently, as my eyes grew accustomed to the light, details of the room emerged slowly from the mist, strange animals, statues and gold — everywhere the glint of gold*". Howard Carter, 1932

In March 1953, 31 years after Howard Carter's astonishing first glimpse into Tutankhamun's tomb, an even more golden treasure was found. Francis Crick and Jim Watson shared that moment of discovery as they looked, for the first time, into the heart of all living things. They saw the structure of DNA, and their vision became the big bang of modern biology.

Francis' life in research began inauspiciously: "*When the war finally came to an end, I was at a loss as to what to do... I took stock of my qualifications — some knowledge of magnetism and hydrodynamics, neither subjects for which I felt the least bit of enthusiasm. No published papers at all... Only gradually did I realize that this lack of qualification could be an advantage. By the time most scientists have reached age thirty they are trapped by their own expertise. I, on the other hand, knew nothing, except for a basic training in somewhat old-fashioned physics and mathematics... I was sure in my mind that I wanted to do fundamental research.... But did I have the ability?*"

Francis Harry Compton Crick was the first of two sons born into the comfortable family of Harry Crick and Anne Elizabeth Wilkins in Northampton, England. Neither parent had been to university, his father running a shoe factory. He was educated at Northampton Grammar School and at Mill Hill School in London — a 'public school' in the English sense — and entered University College, London in 1934 to study physics, obtaining a B.Sc. (second class) in 1937. He started research for a Ph.D. under Professor E. N. da C. Andrade, studying the viscosity of water between 100° and 150°C ("*the dullest project imaginable*") but, with the outbreak of war he moved to the Admiralty and spent the next several years working on the design of magnetic and acoustic mines. It was around early 1947 that he found himself searching for something worthwhile to do. Two areas fascinated him: the borderline area between the living and non-living, and brain function and consciousness. He chose the former. "*It was so late in my career that I knew I had to make the right choice the first time*."

But finding a place to do this in 1947 was not so easy. Randall had set up a biophysics group in London and, when Francis visited his lab, Randall was not keen to hire him: he found Crick "*rather boisterous and (he) talked too much*". Francis eventually found a place in Cambridge at the Strangeways laboratory on the edge of town. His first paper, with Arthur Hughes, was on the viscoelastic properties of the cytoplasm using fibroblasts provided by Honor Fell. They subjected ingested iron particles to changing magnetic fields and looked at how these particles moved in the cytoplasm. They envisaged the cytoplasm as like a "*Mother's Work Basket — a jumble of beads and buttons of all shapes and sizes, with pins and threads for good measure, all jostling about and held together by 'colloidal forces'*".

In 1949, thanks to Max Perutz, Francis moved to the centre of town, to the old Cavendish and the 'MRC Unit for the Study of the Molecular Structure of Biological Systems', joining Perutz and John Kendrew, who were trying to resolve the three-dimensional structures of haemoglobin and myoglobin. Here he found a scientific home; compared to Perutz (pensive and quiet) and Kendrew (retiring, mannered, a real air force officer), Francis was brash, loud and highly opinionated. He was also very clever, but ready to learn — especially from Lawrence Bragg who, with his father, had worked out how to determine molecular structures from X-ray diffraction. From him, Francis learned the key to discovery: identifying problems that were really worth solving.

For those of us who were not around in the late 1940s to early 1950s, it is difficult to appreciate how vague everyone was about proteins, genes and their chemical natures. As genes specified structures in three dimensions it was often supposed that they would contain three-dimensional information. Not much was known about proteins — they were largely regarded as amorphous with no particular amino acid sequence. DNA was certainly not the centre of attention: "*.....at the time, almost no-one thought that DNA might be of genetic interest — it was thought to be associated with genes in some way, but it was not the genetic material*".

A caricature of Francis Crick by Trog, reproduced with permission © *The Observer*.

The quotations in this article are taken from *What Mad Pursuit* by Francis Crick, *The Double Helix* by Jim Watson and *The Third Man of DNA* by Maurice Wilkins.

How Francis lit on DNA is not clear; indeed, in about 1948, he had advised Maurice Wilkins to turn from DNA to proteins! "*Francis….thought I was wasting my time on DNA, and he told me one day, as we sat by the Thames in the Embankment Gardens just outside King's, that he could not understand why I did not concentrate on something useful such as proteins*".

But when Jim Watson arrived in Cambridge in 1951 he found to his delight that Francis also believed DNA was important. They got talking "*for at least several hours a day*". The process by which they came to the correct structure for DNA with the help of the unpublished data of Rosalind Franklin, Ray Gosling and Maurice Wilkins has been told many times. Everyone should read at least Jim's account in *The Double Helix* and see the vivid BBC film *Life Story* (1987), for this is the most dramatic and significant tale in the whole of science. Jim and Francis complemented each other perfectly: although Jim saw how to pair the bases with one another (the kernal of inheritance), Francis understood that the crystal form meant that the DNA helix had to have two strands running in opposite directions — this was crucial for building the model.

The elucidation of the DNA structure did much more than reveal how the sequence is replicated. The double helix implied that genetic information is linear and this linearity had to embody the three-dimensional structure of proteins. The twin strands of logic that this embraced, advanced by Francis, came to be known as the 'Sequence Hypothesis' and the 'Folding Hypothesis': that the nucleotide sequence of DNA encodes the amino acid sequence of a protein, which in turn determines the protein's three-dimensional structure. This was eventually subsumed into the 'Central Dogma' that DNA makes RNA makes protein.

Once his thesis (on haemoglobin) was out of the way, Crick went on to new questions. Typically he did not worry about how DNA replicated — it had to be done by base pairing — but he looked upwards and onwards: if DNA coded for proteins, how to crack the code? And how could the translation of DNA into protein be effected? The background for thinking about these questions was taking shape. In 1955, just a few hundred yards down the road from the Cavendish, Fred Sanger showed that insulin has a fixed and characteristic sequence. Some proteins could be crystallised, and X-ray studies increasingly suggested they had a defined structure. It was also known (Linus Pauling and colleagues discovered it in 1949) that the mutant haemoglobin in sickle cell anaemia has an unusual electrophoretic mobility. Now, in 1957 and under Perutz's wing, Vernon Ingram showed that this mutation causes a switch of just one amino acid.

In the same year Sydney Brenner, who had been encouraged to join the MRC unit by Francis, arrived; the two were to share an office for the next 20 years. Once again, Francis had someone with whom he could mull over ideas. Francis, who thought with great clarity but had a comparatively poor memory, was complemented by Sydney, with his prodigious memory and wild imagination; they made a formidable duo.

A major difficulty in thinking about the code was that DNA is symmetrical (two chains going in opposite directions), yet a polypeptide has a polarity. What drew the arrow? Then there was the obvious coding question, how many bases would specify an amino acid? Although Jim and Francis had privately drawn up a correct list of the 20 amino acids in 1953, the actual number was uncertain. The first code was put forward by George Gamow in 1954 but, although not right, was an essential stimulus. In 1957, Francis, John Griffiths and Leslie Orgel proposed their 'code without commas', a triplet code in which overlapping triplets were unreadable. This code had the great merit of specifying just 20 amino acids and could only be read in one phase. As Francis later remarked, "*It turned out to be one of those nice ideas which is … completely wrong*".

Odile and Francis at their desert house in Borrego Springs, April 2002. (Copyright Peter A. Lawrence.)

Francis worried about how an amino acid could be picked out by only a few bases and saw that, instead, each amino acid might become attached to a specific adaptor nucleic acid. This adaptor would then carry the amino acid to the site of peptide synthesis and choose the correct decoding site by base-pairing. This was a nice idea that was right: and tRNA was discovered by Mahlon Hoagland in Paul Zamecnik's lab in 1958. The existence of tRNA did not help crack the code, however, because now any triplet could in principle code for any amino acid.

There was, perhaps, a hope that one could find a Rosetta stone by observing which amino acid exchanges are caused by which point mutations. Many such results existed, mainly from the human haemoglobins and from the coat protein of Tobacco Mosaic Virus. However, 1961 — an *annus mirabilis* for the code — saw three major breakthroughs. One depended on how different mutagens function: Sydney, Leslie Barnett, Crick and Alice Orgel (1961) proposed in their 'Theory of Mutagenesis' that base-analogue mutagens, such as aminopurine, alter one DNA base for another, whereas proflavine induces mutations by inserting (+) or deleting (–) a base in the DNA sequence. It was whilst mulling

A montage of photographs of Francis Crick taken in 1979 (courtesy of Bradley Smith Productions/Mara Vivat).

over this latter point, lying on a beach in Tangiers in Morocco, that Francis realised that, if there were a triplet code, then three close proflavine mutations (of the same sign) might bring the phase of reading the template back into register. This idea ruined the rest of his holiday. Back in the Cavendish, he set about testing it, working long hours, doing genetic crosses in a blocked off corridor called 'The Gallery', using the *rII* region of phage T4, which had been developed by Seymour Benzer. Around November 1961, he had made the first triple + mutant, and the *rII* function had been regained. The outcome was perhaps the most beautiful paper in genetics: "*General nature of the genetic code for proteins*", by Crick, Barnett, Brenner and Richard Watts-Tobin, which proved that the template is read sequentially from a fixed starting point in triplets.

Of the two other major discoveries of 1961, the first was identification of the template — a transient RNA copy of one of the DNA strands — which brought the information from genome to ribosome and was dubbed 'messenger' RNA. This crucial advance was made by Sydney, Francois Jacob and Matthew Meselson, and separately by a larger group at Harvard. Then, Heinrich Matthaei and Marshall Nirenberg found that a synthetic RNA, polyuridylic acid, when added to a bacterial extract, led to the synthesis of a polyphenylalanine polypeptide. Thus the first codon known was UUU for phenylalanine. Subsequently, the other codons were assigned. Over this period, Francis' dream had come true; and it was he who had been the inspiration and driving force behind the revelations. In his element, he opened the Cold Spring Harbour Symposium on the Genetic Code in 1966 with a review of its history, celebrating his 50th birthday there with a special party organised by Jim.

A year earlier, Crick had presented his 'Wobble Hypothesis' at the Nucleic Acid Gordon Conference. Despite all the excitement surrounding the code, it was Francis alone who worried about how tRNAs could recognise codons in mRNA. Everyone else just assumed it was by Watson–Crick base pairing. But Francis realised that the nature of the code suggested otherwise: there were hints that many codons in which the terminal nucleotide is a U are not distinguished from the similar codon ending in a C; also there seemed to be poor discrimination between A or G in the terminal codon position. Francis realised that an anticodon–codon G–U or G–C base-pair might be indistinguishable if the fit were a bit loose; the same is true with anticodon–codon U–A and U–G pairs, and with anticodon–codon I–U, I–C and I–A pairs (where I is inosinic acid). This hypothesis, which we now know to be essentially correct, was poorly received at the Gordon Conference.

Towards the end of the 1960s, it appeared to many of the founders of molecular biology that the outstanding questions posed in the early 1950s had been solved, at least in outline. The crux of molecular biology — how information flowed from gene to effector — was clear. And the studies of François Jacob and Jacques Monod on the *lac* operon, and of Walter Gilbert and Mark Ptashne on repressors, showed how the expression of this information might be controlled.

Francis and Sydney had wondered over much of the decade which problems to attack after the code was solved: both were inclined to grapple with the logic and mechanisms of animal design, Brenner starting with the nematode *Caenorhabditis elegans*. In 1969, Francis became interested in how tissue patterns are determined, collaborating with one of us (P.L.) and Mary Munro on how morphogenetic gradients might be used to achieve this. He also thought about the relationship between chromosome structure and function and published several papers on the properties of DNA in a supercoiled state.

In 1976, Francis and his Frenchborn wife, Odile, went to the Salk institute in San Diego — this was initially for a sabbatical, but they were persuaded to stay there. In California, Crick continued to seek important problems; he found one, returning to one of his earlier interests, consciousness. This problem has occupied him ever since. He published '*The Astonishing Hypothesis*' in 1994, in which he explains the matter to the general reader. In this area, more than before, he found his rational approach to the subject coming up against clouds of dreamy thinking that emanated from philosophers, the religious and the quacks. Over the last years his enthusiasm shone as ever; last spring Odile and friends went for a walk in the desert, while Francis, parked on a deck chair, in remote solitude, read an obscure paper on neural networks. Attacked by age and disease he nevertheless continued to work unceasingly on a book with yet another long term collaborator, Christof Koch.

At meetings, Francis was an invaluable asset for all. In the discussion at the end of a talk, he had a way of understanding poorly phrased questions: these he would immediately translate for the audience, thereby clarifying a point and sharpening the timbre of the meeting. Some saw this as arrogance, as they also regarded his occasional interventions at large meetings. But this view is an aberration: to those close to him, he was just the opposite. To everyone in the lab, he was 'Francis' (and got very irritated if called 'Dr Crick'). He was friendly and often generous: "*The very amiable Francis, who never condemned anyone except for*

doing poor science (or for being too slow!)....." He could be extremely funny — his jokes were always followed by his characteristic laugh which included a curious way of sucking and exhaling air between teeth and tongue: this mirth was absolutely infectious. He would nearly always attend lab seminars, however dim the title might suggest the talk would be; and he would defend this by pointing out that there was almost always something interesting in the results of experiments, even if the speaker was unaware of it. When tricky political matters arose in the lab, it was to Francis that one would turn for advice. Perhaps most revealing: if he wanted to talk to you he would come cautiously to your lab, see whether you were busy at the bench: if you were, he would wait till you spotted him and then would ask you whether it was convenient to talk and, if not, could you "*pop by later*" to his office when convenient. Conversely, when he worked at the bench, he did not expect to be bothered by anyone.

Francis knew that rank and status have nothing to do with discovery and that seniority and awards can act as barriers between the old and the young. He therefore eschewed honours such as knighthoods. On authorship he believed "*one did not put one's name on a paper unless one had made a significant contribution to it. Mere friendly advice was not enough*". And, interestingly, Jim had the same honest policy.

We wonder why so few have tried to follow Francis' example? He certainly had a surpassing intellect, but there is more to it: his approach demands an independence of thinking that most do not have the courage to emulate. There were other secrets. He sought out problems that were both important and ripe for solution and then stooped on them like a peregrine. Yet all the time he made sure that his ideas were testable and either persuaded others to test them or tried to do so himself. Francis may not always have been in a modest mood, but in his model building he was modest: continually and uppermost in his mind was the knowledge he could well be wrong — an essential part of his toolkit.

Consider his attitude to theory in biology: "*biologists.. often have a plodding and somewhat cautious attitude*". Theorists usually come from the more precise sciences and when entering biology "*are all too apt to look for the wrong sorts of generalisations, to concoct theoretical models that are too neat, too powerful and too clean*". In his book "*What Mad Pursuit*" Francis argues eloquently that biology demands a different approach: organisms had evolved by a series of accidents and, as Monod pointed out, evolution tinkers with what is there, rather than designing things logically from scratch. Having clever ideas about the best way to make a fly's wing, say, is not the way to build a hypothesis that is useful. A good model is one based on a minimal number of facts and inspiration; it must make predictions that are not anticipated but can be tested by experiment. He had an unusual gift for selecting the most telling evidence, and ignoring (for the purposes of theorising) much other apparently relevant data — "*not only can data be wrong in science, it can be misleading*". To accommodate everything, he believed, would require a model to be "*carpentered*" in order to fit. Theoretical biology had to be more than a game: "*I cannot help thinking that so many of the 'models' of the brain that are inflicted on us are mainly produced because their authors love playing with computers.…*".

Another aspect of his unusual nature was his driving curiosity — what is this world that we see around us all about? He knew there is no God and promoted a true scientist's perspective with a near evangelistic fervour. He had a deep interest in how life originated, an interest shared with Leslie Orgel: how could natural selection get to work on molecules produced by prebiotic chemistry? Or could our life have come from elsewhere in the universe? He enjoyed musing about this: how much radiation protection would a spaceship need to carry a primitive bacterium to earth? How might an RNA world have worked? What can we learn from atavistic structures, like ribosomes, that must have been there near the beginning? Several of these thoughts were published. They are fun to read because, however fanciful, they are characterised by his special and incisive attack on the heart of a problem. Although in later years he concentrated on perception and consciousness, he still followed advances in molecular biology.

Francis had superb conversation; funny, insightful, warm and lively, he had the ability to make most things entertaining, simply by looking into them afresh with penetrating clarity. Francis and Odile had many friends and a rampant social life, they opened their charming little home with its "*cheerful, if not playful spirit*" to Jim when he first arrived in Cambridge. Sydney and his family also stayed with the Cricks in Portugal Place when they arrived in Cambridge in 1957. It is remarkable how much time Rosalind Franklin spent with them, at home and abroad; they became part of her own family. This continued long after DNA and up to her death in 1957. These facts tell much more about their home life and deny theories of those who like to imagine Rosalind felt any resentment. Francis and Odile were married for more than 50 years and had two daughters; in addition, Francis leaves a son from his first marriage.

Francis Crick was an intellectual genius, the most original biologist of modern times. He was inspiring, he showed us and many others the incomparable power of science and the scientific method, and as we write this we are overwhelmed by loss and the realisation how lucky we were to learn from him.

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