Book review

A scientist unparalleled

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Francis Crick. Hunter of Life's Secrets
Robert Olby (Cold Spring Harbor Laboratory Press, New York)
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When Francis Crick died in 2004 not that much attention was paid — the event garnered perhaps 1/1000th of the press coverage devoted to the recent passing of Michael Jackson. Future generations will be perplexed: how could we not appreciate that Crick was the greatest biologist of the 20th century, that he found and explored new continents of knowledge that transformed our world forever? Why did we not celebrate that science changes so many things that matter — such that, now in the developed world, nearly all our children survive? People everywhere should want to understand why Crick was so successful at hunting life's secrets. They should be eager to read this, the first thorough biography, by Robert Olby.

Crick's contribution to modern biology was immense: first and foremost, there was the work with Jim Watson, when, using the results of X-ray crystallography obtained by Rosalind Franklin, Raymond Gosling and Maurice Wilkins, the maverick pair solved, by means of model building, bits of cardboard, scruffy sketches, dialogue, logic and thought, the essentials of the DNA structure and saw much of what it meant. Everyone is familiar with DNA now, but non-scientists may not grasp how the structure shines a searchlight into the secret heart of biology. Its importance can be compared with Charles Darwin's discovery of the principle of natural selection, but that discovery looked backwards to our origins and outwards to our place in nature. Conspicuously missing was an understanding of the mechanism of inheritance. By contrast the DNA structure looks inwards to illuminate that mechanism and is the starting point from which we can begin to picture how organisms are built. The understanding of DNA has opened doors to intervention, to diagnosis, to treatment. Exactly fifty years after Crick and Watson's key moment of discovery on February 28th, 1953, I stood with a few others in the drizzle and watched Jim unveil a little blue plaque on the wall of the Eagle pub in Cambridge. Symbolising the value placed on science by most in today's society, we were all pushed off the street by an impatient bus.

Then, there was Francis' definition of the "central dogma", the idea that information can only flow from DNA to protein, and not the other way. It was triumph of logic and insight, which he described in a talk in 1957 to the Society of Experimental Biology. It was here he also first put forward the sequence hypothesis (that the sequence of amino acids in a protein determines its three-dimensional structure) and the adaptor hypothesis (that each of the 20 amino acids would have its own specific adaptor that would mediate between the amino acid itself and the piece of RNA that encoded it). Then, there was the wonderful work with others on the code (exactly how does the sequence of bases in the DNA specify the sequence of amino acids in a protein?). The search was a mix of experiments and theory, and Francis was at the centre of it all the time. During this exciting time, in a collaboration with Sydney Brenner and others, he even worked at the bench and together they solved the general nature of the code, proving with elegant experiments that each amino acid was specified by a triplet (or sextuplet) of bases. This episode culminated in the meeting at Cold Spring Harbor on 8th June, 1966 (Francis' 50th birthday), a famous occasion. Subsequently, Crick went on to think about and contribute to subjects that include the mechanisms of animal development before he settled on the neurophysiological basis of perception, a problem that fascinated him for the last three decades of his life.

When Crick was a boy of about 10 he was already searching for big problems and, no sooner had he thought of one, he worried that it would be solved before he grew up. "*Don't worry Ducky*", his mother said "*there will be plenty left for you to find out*" (Crick, 1988). She was right and he fixed on two questions: What are the elemental differences between the living and the non-living? How does the brain work, particularly when it creates an internal image of the external world? He chose these two topics because they are grand and deep problems, not because they seemed amenable, not because they might produce a nice string of papers for his CV, but because he wanted to do something worthwhile. Thus, again and again and again he checked on himself, on his plans, on his purpose to make sure — as Olby's new biography makes so clear — that his professional life was not wasted on trivia. His colleague Brenner said "*he was not interested in adding another brick to the edifice of science, but in building new edifices*". This approach was highly unusual and is now rare indeed.

There were other unusual aspects of his method, aspects that budding scientists could try to emulate. In *The Unnatural Nature of Science* (Wolpert, 1992) Wolpert argues that using the scientific method and discerning the truth from evidence is an alien mode of thought that we humans have to work at. It is our handicap that we are programmed to base our own views on what others are saying and that we prefer to draw firm conclusions from inadequate data and from divination. We absorb and adopt current opinion without realising it, and it is this fundamental weakness that fuels fashion, as well as giving superstition and religion intellectual wings. To read Olby's biography is to see how successful Francis was in overcoming our natural disabilities; one even wonders if Crick was born without them!

Olby describes Crick as a schoolboy; he was already freethinking with an open-mindedness and an ability to see the signal where others heard only noise. At school his nickname was "Crackers" — which sounds appropriate — for example, he appeared twice in a group photograph by running round the back while the image was being taken. While playing cricket he had the idea of bowling with both arms so the batsman didn't know which hand the ball was coming from. He questioned conventions, developed a strong and lifelong suspicion of bureaucrats (who like to pigeon hole people and cannot cope with eccentricity). He had a quick ability

Francis Crick ca. 1966, for the lab noticeboard. (Photo: MRC Laboratory of Molecular Biology, Cambridge, UK.)

to grasp essentials: during the war when he worked in the Admiralty, the Nazis had developed a powerful magnetic minesweeper and he could see straight away (but his superiors could not) that the answer was to make a subset of special mines of much less sensitivity that would blow up only when under the sweeper and could not be set off at all by ordinary vessels. These mines were very successful, destroying more than 100 minesweepers.

He had a healthy disregard for etiquette. For example the question "*Why are you doing those experiments anyway?*" … "*was to become a trademark of Crick's presence in a seminar*". In the 70s and 80s, I and a colleague, Mark Bretscher, became notorious in following Crick's example and asking this question also — I still feel that it is the first question a scientist should ask themselves — but modern etiquette has deemed it impolite and stifled it. Also, unlike Crick, we nowadays do not confront other scientists in public; there is more often a silent tolerance of all lectures, however much in error they may seem to be. This is damaging; it means that those in the audience who are not specialists (usually most of them) will not know that there are counter-arguments. Some thought Crick was rude in his frankness at seminars; I do not agree, the truth in science is determined and conveyed by data, logic and argument, and disagreeing about the relevance and quality of evidence is right and proper. In this context Olby refers to John Stuart Mill's belief that "*Discuss the issues freely and truth inevitably comes to the surface*". Actually, Crick kept a remarkably open mind in lectures, being as careful not to dismiss as he was cautious to accept and, as Roger Kornberg told Olby, "*he was intent, perceiving every single word without any loss, for he is the world's best listener*".

He made his own decisions, and he was adventurous — for example, he gave up a senior tenured job at the Admiralty to take a grant to start research in cell biology. He was fortunate to be picked out by Max Perutz, who was an amazing talent-detector and hired him for the MRC. This was in spite of the lack of conventional criteria of success, his ham-fisted experiments and Lawrence Bragg's contemporary opinion that Crick was a "*nuisance …. who talked too much*" (Crick, 1988) and "*who overrates his research ability*". Indeed, Perutz had to work hard on the MRC council to get Crick a post. Olby tells us that, in 1951, Crick strongly criticised the work on haemoglobin in Perutz's unit "*they were all wasting their time, he declared*" and advocated the method of isomorphous replacement. "*Bragg was furious*" but shortly before his death Perutz "*recalled the event with pleasure and admiration*" for, as so often, Crick's advice was spectacularly correct.

Another important insight into his unusual thinking is given in this book. There was his reliance on the "don't worry hypothesis", an idea that Olby credited Crick with inventing (although I think the term may have been Brenner's). This is the strategy that one should not be deflected from developing a hypothesis that had

"*explanatory potential*" just because it didn't seem to fit or explain some pieces of data. This idea began early on. Francis and Jim realised that their proposed DNA structure raised a big problem: how could the chains possibly separate during replication? They decided that there must be some solution (which we now know there is, and it is very complex) and they and Georg Kreisel decided to ignore the problem for the moment. It was a strategic and courageous decision and allowed them to go forward.

The don't worry hypothesis came up again in the work with Brenner on the triplet code; there were some results that did not fit: "*In the face of their beautiful theory the moment had surely come to apply the don't worry hypothesis. Brenner explained that under such conditions the theory should remain*" (Olby, 2009); "*And it was wise of us to take all these exceptions, which showed no relationship amongst each other, and put them on one side. We didn't conceal them, we put them in an Appendix*" (Brenner, 2001). And this strategy relates also to Crick's usage of models. He consciously tried to solve problems with different *minimal* sets of evidence, because any theory that fitted all the data might "*be misleading if not plain wrong. A theory that did fit all the data would have been 'carpentered' to do this and would thus be open to suspicion*" (Crick, 1988). The idea of using minimal sets follows logically from two facts, one that models can be built more clearly with small numbers of starting conditions and two that, especially in biology, single experiments are often deceptive. He organised his and colleagues' experiments well; when asked how he did it he said they had not been really planned but were "*logically improvised*", hinting I think at the importance of getting the right mix of theory and experiment, a crucial and difficult matter for all scientists.

Olby's book also reminds often that when one is trying to solve a new problem you have no idea of the answer, so obvious yet difficult to bring to mind when we look back from the light into the darkness. For example, when I give lectures touching on the DNA structure, I show a film of one of the key moments of discovery. This film is a clip from the BBC drama-documentary *Life Story*. We see Jim Watson fiddling with cardboard cut-outs of the four bases on a table. He can't see how to put them together, but the audience can — because they know the solution! So they laugh at what they see as his obtuseness. However, when we confront a new problem, we cannot see how lost we are (until one day the problem is solved, usually by someone else).

Crick deep in the Anza-Borrego desert in 2002.
Francis was too ill to walk and Odile Crick and I left him reading a paper on neural networks. He was still studying it when we returned two hours later. (Photo: Peter Lawrence.)

Crick had "*no time for privileged rank and snobbery*", no time for the trappings of celebrity, for "*gracing fashionable banquets*" nor for the distractions of fame. He spent all his life, as much after the Nobel as before it, hunting life's secrets and this devotion to science is well documented by Olby. But his character often brought him into conflict not only with received opinion but with others, he lacked tact, he sometimes could not see that others might not welcome his abrupt intervention into what they thought of as their scientific territory. The matter of the use of Franklin and Gosling's data in the building of the DNA model still reverberates nowadays and is discussed here in more detail than I have seen anywhere — it constitutes a fascinating ethical dilemma. Olby remains a dispassionate observer, even though one thirsts for his opinion.

Crick's openness and lack of gentility got him into trouble on occasion. There was the famous case of his resignation from Churchill College over the building of a chapel. He felt strongly that there were already plenty of places of worship in Cambridge and that it was not appropriate for a modern educational institute to add to those. Olby has dug out some splendid letters in one Crick tried to expose the hypocrisy of college non-believers having their children christened, "*which seems to me to be ridiculous. One can only conclude they regard Christianity as a completely harmless set of beliefs and that they tolerate it as one might humour a somewhat eccentric aunt… although Christianity is no longer virulent, it is surely not yet harmless*". I could add, although perhaps I shouldn't, that there is a related myth that is perpetuated nowadays by the well-meaning; it maintains that somehow a scientist can find room for belief in the supernatural and that many excellent scientists are religious. In my experience biologist believers are almost as rare as the passenger pigeon.

More dangerous was his flirtation with eugenics, which began with a famous lecture he gave to the Cambridge Humanist Society in 1968; there he broached a number of tricky subjects, including overpopulation,

the right to bear children and euthanasia. He wrote "*we are surrounded by Barbarians… who cling to the old knowledge…… They cannot stomach the idea of Nature evolving in an open-ended way without any foreseeable target*". This latter was also Darwin's problem. However, the response to Crick's lecture frightened him and he didn't dare broach these subjects in public again.

The heart of Olby's book is the long section on the code; it is carefully researched and written in a style that allows the science itself to drive the narrative, it is absorbing and captivating. In this section, Olby takes us into the depths of the unknown and describes well how Crick and others fought their way up to the surface. Olby also succeeds in placing Crick's hunt in the context of contemporary knowledge and tells us the opinion of the doubters of the time. Here one is reminded of the importance of ideas and arguments in science. One is forced again to see how easily ideas can be drowned by data. Olby also makes serious attempts to explain difficult areas such as the principles of X-ray crystallography and the problems of consciousness. I am sure that I don't fully understand them now, but Olby took me further along the road. The writing is pleasant and easy to follow, a nice mix of detail and reflection. Sometimes the detail given may seem excessive (it is a long book) but almost imperceptibly one becomes more and more familiar with its subject. He does very well in documenting and explaining the growing case for DNA as the hereditary material and how Crick found and understood that evidence. So it is more than the biography of one man, it is a biography of ideas and this is one main virtue of the book.

I suspect the book is not always accurate about detail — I know the small part where I feature contains several major errors but I expect and hope the important sections are more accurate. For example, I am not sure it matters too much that Boris Ephrussi was described as a Polish scientist (he was a Russian émigré).

How to compare the two biographies of Crick so far published? Matt Ridley's book (Ridley, 2006) is briefer, more accessible and more popular, it is written with style: of Crick's 50th birthday, Ridley gives us a poetic summary: "*On that day Crick stood on top of the scientific world. Others had done some of the crucial experiments in the decoding of the code, and others had shared the excitement of vital discoveries along the way — the messenger, the adaptor, the triplet nature of the code — but Crick had been there at every step, the dominant theoretical thinker, the best guesser, the indefatigable sceptic, the loudest debater, the conductor of the scientific orchestra.*" Olby's biography does not indulge in these enthusiastic outbursts; but perhaps better it explains clearly how and why 8th June, 1966 was Crick's day. We know already the drive, the false turns, the determination and the ambition that brought solutions to the secrets of life. We know them because Olby has told the scientific story so well, he explains the ideas, the data and the changing viewpoints step by step.

Francis' philosophy of not putting his name on the papers of others unless it was really earned was an important one, especially nowadays when many so-called authors do not know enough about how the results were obtained to take any real responsibility for a paper's contents. This philosophy began early — Watson chose to be first on the initial DNA paper and Crick was content; authorship of the next paper was decided by the toss of a coin, which Watson won even though Crick "*almost entirely*" wrote the paper. Francis kept true to this principle: the last time I talked to him, not long before his death, he explained why he would not author the forthcoming book by Christof Koch *The Quest for Consciousness: A Neurobiological Approach*, even though it was the outcome, in part, of a long and intense collaboration between them. He told me he wanted Koch to have the credit for the work, "*Because, you see, I will not be here*". For me Francis is still here, not only in the great discoveries he made that have changed and will change our world, but also as an inspirational example of how to live life to the full, as a scientist.

Postscript

To find another view, beautifully articulated, of Francis Crick there is the shorter biography by Matt Ridley (Ridley, 2006). The Wellcome Trust has Crick's papers in an archive: http://genome.wellcome.ac.uk/node30074.html. Martin Packer created a website in honour of Francis that is now an extensive source: http://www.packer34.freeserve.co.uk/rememberingfranciscrickacelebration.htm

The whole story of DNA and the code is written in fascinating detail in *The 8th Day of Creation*, by Horace Freeland Judson (Jonathan Cape, 1979 and reprinted by Cold Spring Harbor Press, 1996). There is a fine biography by Brenda Maddox *Rosalind Franklin: the Dark Lady of DNA* (Harper Collins, 2002), while there is the autobiography of James D. Watson *Avoid Boring People: Lessons from a Life in Science* (Random House, 2007). In addition, of course, he wrote the contemporaneous and sparky *The Double Helix: A Personal Account of the Discovery of the Structure of DNA (*Touchstone, Rockefeller, 1968). Sydney Brenner has produced a lively mix of reminiscences, opinion and wisdom in *My Life in Science* (2001). Maurice Wilkins's autobiography *The Third Man of the Double Helix: The Autobiography of Maurice Wilkins* (Oxford University Press, 2003) gives his side of the story and insight into how Francis became interested in DNA as well as telling us about Randall's part in Wilkins's crucial misunderstanding about the role of Rosalind Franklin at King's.

In 1987 the BBC produced an authentic story of the DNA discovery/tragedy (Rosalind Franklin died in 1958), as a drama-documentary *Life Story* (or *The Race for the Double Helix*). The direction, screenplay, dialogue and acting are all superb and for those wanting accessible images of the discovery and the logical steps that lay behind it, this film, which can still be obtained, could not be bettered.

References

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