Francis Crick: A Singular Approach to Scientific Discovery

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Francis' office window (at the Salk) commanded a panorama of the Pacific. "This grand natural scene was a physical correlate of Francis's intellectual world: wide-ranging, brilliantly lit, a little overawing, but also immensely inviting and above all an exciting place to be." (Mitchison, 2004).

Francis Harry Compton Crick was born 100 years ago. He was an inspiring man whose scientific strategy was golden in its success (Olby, 2009). He was remarkable, not only because of what he discovered but for how he set about discovery. According to his own account (Crick, 1988) as a little boy he was already searching for big problems in biology. Later, he settled on two questions that anyone could ask, questions that arise more from observation and an open-minded curiosity than from a specialized education. The questions were basic: first, what distinguishes the living and dead, i.e., what processes are the essence of life? Then, how does the brain work, for example to create a perceived and internal image of the external world? He chose these two everyday questions because they are deep and difficult and he must have wondered whether they would ever prove to be answerable. All his life Francis was a serious and committed scientist; he aimed high and tried to make sure his professional life was not thrown away by working on trivia. This was, even in those salad days of molecular biology, an unusually ambitious approach to a career in research.

Francis' collaboration with the much younger Jim Watson, as well as their interactions with Rosalind Franklin, Raymond Gosling, and Maurice Wilkins—including their use of the images and measurements that these London-based scientists had made—constitute the most dramatic story in the history of science; surely this tale will always be the stuff of dreams for young scientists. And their methods were very different from the "big science" of nowadays with its heavy dependence on number-crunching computers and the resultant slag heaps of data. Their approach to the DNA structure was stuttering, conversational, disputational; their technical aids were chalk, blackboards, scissors, cardboard, bits of wire, shapes of metal and rulers. It worked partly because of the creative mix of Francis' deep understanding of X-ray crystallography with Jim's moxie and determination. Looking back at this seminal collaboration Francis pointed out "We were not the least afraid of being candid with one another to the point of being rude. If you don't have constant interchange …. and say what you think of the other person's ideas to their face, then I don't think you can solve problems of this kind" (Crick, 1973).

Their moment of discovery, when they first saw clearly the structure of DNA, occurred on a Saturday morning, February 28th, 1953. It was then that Jim, fiddling with cardboard cut-outs of the bases, saw that an A-T pair filled exactly the same space as a G-C pair. It must have been so exciting to appreciate the structure's significance and its beauty and to know that no one else had ever seen it! They probably felt like Howard Carter when he peered into Tutankhamun's tomb and saw the glinting treasure. No wonder they rushed off to the Eagle pub to celebrate, and I can imagine how boisterous Francis must have been.

Exactly 50 years later, I and a few others stood outside the Eagle pub in the rain while Watson unveiled the blue plaque (Figure 1). Increasing numbers of tourists now come to view this plaque but I wonder how many appreciate that it marks the moment when our understanding of the natural world, as well as the limits of medicine, changed forever.

Francis' next main contribution was his lecture to the Society of Experimental Biology in September 1957, published in 1958 (Crick, 1958). Francois Jacob was at the lecture: "Crick (…) talked incessantly (…) breaking up his sentences with loud laughter (…) setting off again with renewed vigour (…) at speed (…) Crick was dazzling" (Jacob, 1995). Reading "On protein synthesis" (Crick, 1958) now with the clairvoyance of hindsight is an astounding experience because he turned out to be correct in all his main conclusions. The logic and arguments are clearly presented in an open and honest style we will never see again—indeed, I think today's picky and partisan reviewers might condemn the paper as too speculative. In the lecture, Francis launches three main hypotheses which are now part of everyone's understanding of biology: the sequence hypothesis, the adaptor hypothesis, and the "central dogma." There is also a sea change in that lecture; he shifts the focus of everyone's attention from molecules to information. Where is the information? It's in the nucleic acids. How does it pass from the DNA into the protein? Via the mechanisms of protein synthesis and what Francis called "sequentialization." Could it go the other way, from protein to DNA? No.

Nowadays, with the misplaced obsession that makes *where* one publishes more important than *what* one publishes, this paper might not have had so much impact. Fortunately, in the 50s and 60s such metrics had not yet been concocted—the damage they do now is partly because they tend to value experimental work (however bad) over ideas (however illuminating). Crick's 1958 paper is now widely recognized as a triumph.

Figure 1. The Eagle Pub in Cambridge, England

At least as important was his work on the code (how the sequence of bases in a piece of DNA specifies the sequence of amino acids in a protein), which took several years, and during this exciting period he worked vigorously at the bench. The hunt to crack the code involved many scientists; it was international and competitive and was a mix of experiments and theory. Both genetics and biochemistry were employed, and Francis was always excitedly involved (Cobb, 2015). The successful ending of this search was marked by a meeting at Cold Spring Harbor on 8th June, 1966 (Francis' 50th birthday), described beautifully by Matt Ridley:

> "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." (Ridley, 2006).

Francis' return to doing experiments himself was ephemeral and fevered. However, he was very successful; he, Sydney Brenner and others had realized that proflavin mutants, unlike other mutagens in use at the time, either added or deleted a base. As he relaxed on a beach in Tangiers he was hit by an idea so irresistible he just had to test it by experiments. This led to the iconic paper by Crick, Brenner, Barnett, and Watts-Tobin that revealed fundamental aspects of the code, all in the absence of any DNA sequencing (Crick et al., 1961). They combined pairs of acridine mutants and were able to classify each of the mutations into one of two classes (plus and minus) by their phenotypes when assessed alone and in combination. They then combined them in different sets and found that, for example, while one or two plusses damaged gene function, three plusses often restored it. They therefore deduced that the code is read three bases at a time, that there are no commas and that reading likely begins at a fixed start point. Further they worked out, because nearly all of the codons could be read, that the code was likely to be degenerate. A spectacular example of the power of combining simple experiments with thought. Later, Francis recalled the excitement and remembered looking at the plates in the afternoon, seeing the plaques and saying to Leslie Barnett "you realise you and I are the only people in the world who know that it's a triplet code" (Crick, 1993).

Francis' spell at the bench was important to him; he often referred to it afterwards and I think it served to remind him how difficult, repetitive and fraught the experimental world is. Useful, as he spent much of the rest of his life in fruitful and mutually beneficial collaborations with experimentalists whose trials and tribulations he could sympathise with.

After 1966, Francis felt that molecular biology was mined out and he "found himself with most of my ambitions satisfied" (Crick, 1988). Therefore, as he did not want to be part of a mopping-up operation, he set out to search for a new problem. He was aided in this by Brenner, and these two outstanding scientists undertook an intellectual and technical exploration of embryology. They both gave genetics the central position it deserved and this was innovative because, by the 1960s, genetics had become rather a dry numerical study of inheritance and was undervalued; indeed "many people went into genetics simply because the problems they were working on were insoluble" (Brenner, 2001). Few people appreciated that the main task of genes is not to make an animal tick, but to *build* it. Also, at that time, embryology was partly a whimsical semi-philosophical subject, characterized by ill-defined and abstract concepts. The two fields were so different that an amicable and productive marriage between them was impossible—consequently, developmental biology, as embryology came to be rebranded, had to be reinvented with new tools and new thinking. Brenner's crucial contribution here was both imaginative and reductionist. He looked for a new model organism for embryology, one in which the generation time was short and the genetics tractable (after a flirtation with a rotifer, he settled on the little nematode worm, *Caenorhabditis elegans*, whose life cycle is only 4 days). It was a brave and original decision. We do not know Francis' contribution to his choice, but I do know Francis and Sydney shared an office throughout this time, and on their blackboard was a big note saying "Reading Rots the Mind" and that they talked about science nonstop. "We liked simple chalk and blackboards.... we would meet, often every day and talk about anything and everything. We would talk about an experimental result and ask, 'what could this possibly mean?'" (Crick, 1988). Most scientists nowadays do not think they have time for such rambling discussions, they are too busy with committees, with experiments, with trying to persuade a highly rated journal to accept their latest offering, with anything except examining the heart of their subject. Yet, Francis' and Sydney's approach was so valuable: for example, the nematode project has resulted in many discoveries—already six people have been awarded Nobel prizes for their work on *C. elegans*.

I collaborated with Francis for a few years in the early 1970s, in the field of developmental biology. We were interested in how gradients of diffusing molecules might specify positional information and planar cell polarity (Lawrence et al., 1972). I remember most his ability to get to the principles as well as his inability to remember nearly all the details. My role in the collaboration was to do the experiments, to present data to him and to keep him tied to that data, as well as being an interlocuter. This ability to keep to the heart of a problem was very characteristic of Francis. I remember once, when he was introducing my lecture about our work, he asked the audience not to worry about the notes, but to try to follow the music. This emphasis on sifting, classifying, categorising information was very important to the way he thought about science. For example, consider when we were collaborating on the subject of planar polarity. The important fact about planar polarity is that there is an arrow that is drawn in the plane of the epithelial sheet consistently, across each of several or many cells and this gave coordinately oriented bristles or cilia. Francis knew that this problem was not to be solved by a hypothesis that just required a few genes to act on each other in some kind of "pathway," it is essentially a spatial, contextual problem. Concentrating on the big picture meant that he always managed to forget that the bristles pointed backward. For him, the key fact was that they pointed like an arrow, the direction was far less important.

Another extremely important insight into his thinking is given in his autobiography (Crick, 1988). He discusses a way of using models which is counterintuitive, but Francis made it work, spectacularly. When you are trying to solve a new problem, you have no idea of the answer—obvious of course, but often forgotten when we look back at problems that we or others have solved. But when faced with a new problem it can be like being in a dark room with no knowledge of whether there is a way out and, if there is, where it might be or what it might lead to. Francis would try to solve such problems by using different subsets of all the available evidence, the choice of which bits of data to include in each test subset would be by trial and error, plus, no doubt, some intuition. He explained that any theory that fitted all the data "was bound to 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). This idea of using minimal subsets follows logically from the realization that, especially in biology, it is "important not to place too much reliance on any single piece of experimental evidence. It might turn out to be misleading as the 5.1 Å reflection undoubtedly was" (Crick, 1988). I think more should try to emulate Francis' strategy. It is not a natural method, but it can be very effective; it helps a scientist to look beyond and through confusing signals to see the wood and avoid bumping into the trees.

Then there was the "don't worry hypothesis," a term that I think was Brenner's. Often when one builds an explanation that ties together a bundle of findings and makes sense of them, one can get hung up on something. It may be a new observation that does not seem to fit in or a counterintuitive consequence of where one is going. For example, Francis and Jim worried about how on earth the double-helix DNA might replicate, how could it unwind? By deploying the "don't worry hypothesis" they could just put that concern aside and get on with thinking about the structure itself. As it happened DNA replication proved very complex and that decision was a wise one.

Descriptions of discoveries do not give much of a picture of how it was to work with Francis and to interact with him in conversation. So it might help the reader for me to try to do this. Looking back, I remember a courteous and congenial person, lively and enthusiastic, with a strong and essentially serious interest in everything, including things that were mainly just good fun. There was a sharp almost forensic mind, always vigilant, always on the lookout for something of interest, something to laugh at, something to entertain, something to lead to a new idea or a new perspective. Francis usually took a charitable perspective on others; if someone gave a talk, well the work might appear to be badly designed and presented but, you never know, there could be something in there that would be worth noting. So listen and watch out for that spark! But he also had a very active quack-detector, and this would instantly pick up the mumbo-jumbo of religion or the least sign of superstition. For him (and for me) there is no place for mysticism or the numinous in our wonderful world, far better to try to understand it by means of evidence, logic, and argument.

Francis' collaborations were always with people younger than himself, and they lasted. Why? First, his personality made the process of discovery, both success and failure, enjoyable. Second, scientists, often tending to obsessions, are generally poor at communication and empathy, but Francis was an exception; he patiently explained his ideas to others. Third, Francis had a policy not to author papers unless his contributions were substantial. For example, when we wrote a paper together in 1975 that was published in *Science* it was a truly joint effort (Crick and Lawrence, 1975). Neither of us could have written it without the other. At that time Francis had a Nobel prize and a huge reputation, while I was a very junior postdoc. Nevertheless, he asked me to decide on the authorship order. Over many years I have consistently found that this kind of consideration cements collaborations. Shortly before he died we discussed the book that he and Christof Koch were writing. He had worked over years with Koch on this book, yet he wanted Koch to have all the credit "because, you see, I won't be here."

Francis enjoyed life; his interest in nature and his almost childlike curiosity were maintained to the end. He and his wife Odile (Figure 2) had developed an affection for the desert, and living as they did in San

Diego, California, the Anza-Borrego desert was not so far away. Long after most people would have been retiring to their living rooms and watching bad TV, Francis and Odile decided to design a desert house. Their idea was to have a bungalow in which each room had a large inward-facing window that overlooked a central garden. As in Japanese ryokans, each of these windows saw only garden, they did not give a view into any other room. Odile was a fine artist, she painted mostly portraits, but she also had superb taste, and the house was beautifully decorated in African craft. Outside the front door there was a little statue and a heart-shape and their initials made up by lines of little stones. It was a lovely place, somewhere to reflect on two lives that had been shared for 50 years, on the beauty of nature, much of it made possible by the invention of the nucleic acids.

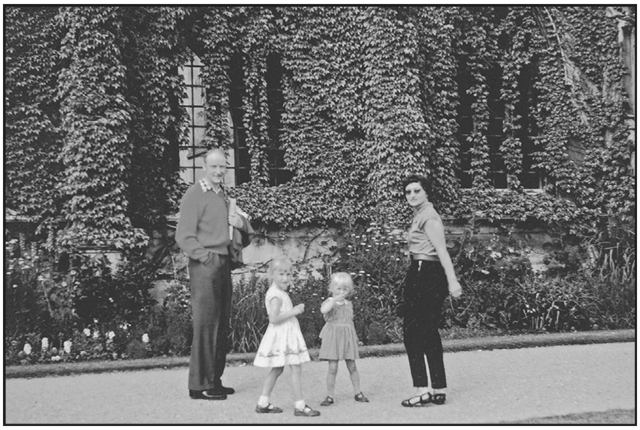

Figure 2. Francis Was also a Family Man
Here he is in Cambridge, probably in 1957, with Gabrielle (b 1951), Jacqueline (1954–2011) and Odile (1920–2007). Photograph by Maury Fox. Courtesy of Pauline Finbow.

Are there lessons for us today? I think so; Francis identified and persisted with large apparently insoluble problems, and he and his colleagues (Max Perutz is a fine example) succeeded. He followed Darwin's advice: "Let theory guide your observations," otherwise one "might as well go into a gravel pit and count the pebbles and describe the colours" (Darwin, 1903). Young scientists today need to aim higher, and I do not mean better journals, I mean newer, larger problems, more risk-taking and a sense of adventure. That is the only way in the creative world; in the long run one gets nowhere by exploiting the obvious, however pragmatic it may seem at the time.

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