Commentary

Critical fun with Francis Crick

"I have never seen Francis Crick in a modest mood". This was the way Jim Watson began his controversial book *The Double Helix*. No wonder Crick felt taken aback by such seeming lack of solidarity towards an old friend and colleague – after all, they had together conquered the Everest of biology, opened up a new field of inquiry about the structure and function of the gene, and touched on the very nature of life. And this was just one example of Watson's snap judgments and indiscretions; there were more in a widely circulated early manuscript of the book, entitled "*Honest Jim*". In fact, few people in the manuscript or subsequent book escaped Watson's "over-honest" commentary – least of all himself.

But it was the overall way in which Watson presented the story of the race for the double helix that galled Francis Crick and also Maurice Wilkins, Watson's co-laureates for the Nobel Prize in 1962 (Watson and Crick shared a half, Wilkins got the other half for his X-ray crystallographic work). Crick and Wilkins regarded this as Watson's highly personal version of the truth, and a book that could do potential damage. Their pressure on Harvard University Press not to publish *Honest Jim* succeeded, but the book could not be suppressed. The result was a somewhat less gossipy version, *The Double Helix*, published by Atheneum Press in 1966.

Crick's and Wilkins' reactions were not at all unusual at the time – in fact, book reviews of *The Double Helix* show that many were shocked at Watson's descriptions of how the work was done. The 1960s was an innocent time when it came to the public image of science. (Later, Crick and Wilkins reconsidered and reconciled with Watson, allowing him this "personal view".) In his book, Watson often does make it sound as if Crick and he were just lucky, stumbling on the truth while using other people's knowledge. Crick in his own memoirs notes that Jim Watson and he certainly could have used "the logical approach" had it proved necessary, and briefly outlines how they would have gone about this.

What might Watson have had in mind with his statement about Crick? Crick certainly had a very tangible presence. As a youngish man in his mid-thirties at the time when Watson met him, Crick was known for his loud laughter – so loud, that the director of the Cavendish Laboratory, Sir Lawrence Bragg, often hastened away when he heard it. The pictures one sees of Crick makes it easy to imagine him actually laughing most of the time. He loved to dream up theories and experiments and to criticize others. But his laughter was not malicious; it was a sort of general laughter of enjoyment, the excitement of exploring new avenues, of overcoming new challenges, of pushing the unknown – in short, the laughter of a happy scientist.

Crick was enjoying himself tremendously dreaming up explanations, often for other people's work. He walked into colleagues' labs telling them what kinds of experiments to do and what theories of his those would support. He talked endlessly. Meanwhile, he had no obvious authority to stand on, not having his Ph.D. Bragg wanted him to stop distracting himself, get on with his own thesis work and get out!

Crick was in some sense more of a "pure" type of scientist than many others, because he had in fact given up an offer of a permanent career with the Admiralty after the war. Crick was originally a physicist but like many of his colleagues got disillusioned with the direction of post-war physics and moved into the field of biology instead. For Crick as for many of his colleagues, their fellow physicist Erwin Schrödinger's *What Is Life* had been a clear inspiring factor. One of the things that especially resonated with Crick was Schrödinger's discussion of codes. He was fascinated by the way in which a limited number of elements could give rise to a great number of combinations (the example given was the Morse code). This was to come in useful later.

Crick had that kind of mathematical brain that likes calculation and puzzle-solving. That served him well in his own Ph.D. research on proteins, because he had to determine three-dimensional structure based on delicate calculations of intermolecular distances using X-ray crystallographic methods. But

his ever-active mind was easily distracted by other people's promising-seeming puzzles – an oddity which sometimes resulted in joint publications.

For the more laid back at the Cavendish, energetic Crick may have been something of a nuisance. But he soon found someone who actually enjoyed talking with him – Jim Watson, then a 23 year old postdoc. And they talked on, so loudly that when a small lab happened to become available, it was given to them. It soon became clear that neither of them wanted to do the work they were actually supposed to at the Cavendish and that both were fascinated by DNA.

The work of Watson and Crick on DNA took many forms and many wrong turns. Sometimes they had to work in secret, having been forbidden to pursue DNA further. The interesting thing is that their work consisted largely of talking. And talk they did – in the lab, outside the lab, in pubs, on walks, at parties, and at Sunday luncheons arranged by Crick and his French wife Odile. The project became an increasingly social affair, as visiting scholars and scientific luminaries passing through were routinely consulted for advice. Crick and Watson together developed a surprisingly efficient approach. They would often uncritically brainstorm about possibilities, whereupon they switched gear and ruthlessly scrutinized the result – of themselves or of each other. Both men appeared to have an unusual tolerance for criticism, in the sense that they were able to disconnect the critique from the person behind it – an ideal situation in science but seldomly achieved.

After their initial discovery, it was Crick rather than Watson who was to uphold the spirit of excitement of further investigation into the mysteries of the genome. Ever an explorer, Crick led the unraveling of the workings of transfer and messenger RNA, formulating what he called "The Central Dogma" (the view that information always travels in the direction of DNA to RNA to protein, never in reverse). With the dogma in hand, enthusiastic Crick inspired a whole generation of scientists to focus their interest on the new field of molecular biology. He gave lectures to important groups of scientists at leading research centers and wielded his influence especially at the famous Gordon conferences, informal yearly gatherings in New Hampshire around topics of current interest. Participants at these conferences were exposed not only to Crick's insights but also to his particular thought style. Crick was also an avid letter writer, and his role for the emerging molecular biological community may have been something like that of Father Mersenne in early modern science (Mersenne worked as a liaison between scientists and general commentator at a time when no formal journals existed). An interesting sidelight here is that Crick apparently misunderstood the meaning of "dogma" (something that Jacques Monod later pointed out); he did not think of it as an absolute notion but more as a theory. Be that as it may, the Central Dogma as perceived may have had a useful organizing function on research at the time. (The dogma was later shown not to be so absolute – in the early 70s Howard Temin and David Baltimore were to get a Nobel prize for their discovery of reverse transcriptase.)

The next obvious step was the unraveling of the genetic code. George Gamow had already theorized about its possible nature, but it was not until 1966 that Crick together with his new collaborator Sydney Brenner was able to experimentally demonstrate that it was indeed a question of three bases (codons) coding for each of 20 amino acids. Crick, in typical style, had earlier himself played with various mathematical solutions to the problem, coming up with a perfect-seeming "commaless code", which got published in the *Proceedings of the National Academy of Sciences*. It just happened to be wrong. Other times, however, Crick's molecular biological-mathematical intuition produced the correct result – especially his prediction of the necessity for site-specific "adaptors" facilitating protein synthesis. As Crick reflected himself, when we are dealing with the products of evolution, theory and logic are never enough – empirical checks have to be made.

There is no doubt that pioneering molecular biologists had a lot of fun. They could now use their theoretical and critical skills to solve ever more puzzles – and puzzle-solving was what they liked to do anyway! This fun could take unusual manifestations, such as the RNA Tie Club, an idea of the ever active George Gamow's. It appears that the club actually never met, but it was useful as a way to circulate members' papers, and some publications even came out of it (like Crick's "commaless code"). The club was limited to 20 members, one for each amino acid, and each member had his own tie and a pin representing the corresponding three letter abbreviation. Crick himself was a Tyr.

While Watson became more and more of an administrator, Crick continued following his inner drive. He wanted to explore the unknown and push the limits of science as far as possible. For him there

were two areas worth investigating: the nature of life and the nature of consciousness. Both operated at the boundary of the living and the nonliving, and this is where he wanted to situate himself as a researcher. In the mid-1970s, moving to the Salk Institute in California, Crick started a brand new career as a theorist of the mind. At the Salk, Crick again used his well-tried method of trying to make theoretical sense of available data. He also occasionally collaborated with others, for instance tackling the origin of life together with Leslie Orgel. Because for Crick, science actually meant more than puzzle solving and fun. Through science it would be possible to establish a solidly material – chemical and physical – basis for such metaphysical things as life and mind, and even the soul. Crick did not have much tolerance for religious explanations.

It is unusual for someone to be able to follow his own quest to such an extent as Crick. One of the "secrets" behind Crick's early success was clearly the financial support he was obtaining from his uncle Arthur Crick, a fact which he gratefully acknowledges in his memoir (which also sports a photo of his smiling uncle).

The impact of molecular biology on twentieth-century science clearly consisted of more than the discoveries in themselves or the opening of a new research field. Molecular biology encouraged a whole new thought style in regard to biology, a more daring but at the same time more critical one. With the success of molecular biology, it was not enough to make vague pronouncements: the proof was in the pudding, things could be calculated, experiments made, hypotheses tested. In fact, so much calculation, thinking – and criticism – could go into the discussions of potential new genetic phenomena or mechanisms that the discussions came to serve as an useful form of collective "dry labbing", speeding up the process of reasoning and design of clever experiments. In a sense, it was nothing but a quick and tangible version of two combined ideas of Karl Popper's: science as the result of conjectures and refutations, and scientific truth as an intersubjective achievement, accomplished through critical discourse. Crick himself definitely saw criticism as an integral part of Watson's and his success. He wrote that "[i]f we deserve any credit at all, it is for persistence and willingness to discard ideas when they became untenable."

The "critical style" of the molecular biologists was soon to collide with a more traditional style of "scientific story-telling". At least according to the zoologist Edward O Wilson, the relative success of molecular biology soon led Watson, his young colleague at Harvard, to sneer at the "softer" field of natural science, leading to what Wilson calls rightout "Molecular Wars" in the 1960s and 70s. In fact, Wilson's own controversial tome *Sociobiology* was his response to the threat from the Watson camp, who wanted natural history booted out. Wilson's aim was to strengthen evolutionary biology's central achievement at the time, The Modern Synthesis, by bringing in recent theories about the evolution of behaviour as well, and to do this in a maximally mathematized form, using population and behavioural genetics.

It was probably not the fault of sociobiology if its hypothetical genes in people's imagination were equated with the spiral staircase of DNA and taken as actually existing! However, general "gene talk" was certainly a leading concern in the late 20th century's sociobiology controversy, where critics accused sociobiologists of genetic determinism. (Ironically, however, there does exist a reverse feedback loop between Dawkins' idea of the selfish gene and DNA. Inspired by Dawkins, Crick and Orgel published a paper entitled "selfish DNA" – their term for the extra "junk DNA" that nobody seemed to know what to do with at the time.)

Another more direct consequence of the success of molecular biology and the genetic code was the overall focus on the gene itself. A kind of blueprint thinking came to prevail: the gene was seen as the active agent, and the process of gene expression and the factors involved there were largely played down. At the time, this concentration on the gene was probably natural. After all, science is the art of the soluble (Peter Medawar), and the molecular biological community were intent on tackling particular problems of DNA and the workings of the genetic code.

The "gene-as-blueprint" image stuck, however, and later found its way into much early discussion around the Human Genome Project (of which Watson was the first director). It took such things as the recent realization that the action is in the proteome rather than the genome and that the proteome is sensitive to stereochemical factors, or that much-touted gene therapy often has not worked (because the inserted gene needs to be in the exactly right place to do its job) for serious new interest to develop in

the "working conditions" of the gene. Recent attention to the way in which the genome regulates each gene's actual activity has led to research into various types of regulatory DNA involved in transcription (for example promoters, enhancers and silencers), and how their effects may be connected to such factors as spacing and order of binding sites. The general public, however, may still think in terms of "the gene", that deterministic-seeming icon of DNA, especially as much quasi- or real religious rhetoric was connected to the gene and genome.

Meanwhile, the paradigm now is shifting away from the focus on the gene towards the various factors within the genome that regulate gene expression in development. A new "second genetic code" – that of gene regulation, is now the next big puzzle to solve, a seemingly much more complex one than the working of the double helix. But perhaps there is a shortcut even here, as Crick might have been the first to suggest. Crick is not around to help us this time – and in any case, he reluctantly disconnected himself from the genetic code as he moved on to Salk and the problem of consciousness. Still, I am sure that Francis Crick would hope that the many different scientific teams now engaged in evo-devo research are having as much fun in their critical discussions and deliberations as he once had together with Watson and other colleagues.

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