Obituary

Francis Crick (1916–2004)

Alexander Rich and Charles F. Stevens, respectively an early collaborator of Crick's and a long-standing colleague at the Salk Institute, describe the life and work of one of the great thinkers of twentieth-century biology.

Alexander Rich writes:

Francis Crick, who died on 28 July at the age of 88, was trained as a physicist but became arguably the most influential biologist of the twentieth century. His great curiosity was coupled to highly original thinking; through force of intellect he obtained answers to many fundamental problems. In seminars he often demanded clarity from speakers, thereby generating some tension. However, he had a lively sense of humour, sharp but never malicious. Crick had no PhD students and only a rare postdoctoral fellow, but nonetheless often worked closely with a collaborator. Above all, he was a very kind and considerate person.

Born in Northampton and trained at University College London, Crick started graduate work in physics at the beginning of the Second World War. His "unimaginably dull" thesis project was to define the viscosity of water at high pressures. In a career-altering episode during the Battle of Britain in 1940, a bomb fell through the roof of the physics laboratory and exploded on his instrument. Crick then went to work for the Admiralty, designing 'clever' mines. He started biological research in 1947, working initially in the Strangeways Laboratory in Cambridge, where he devised experiments to measure the viscosity of cytoplasm. This left him somewhat dissatisfied, and in 1949 he joined Max Perutz at Cambridge's Cavendish Laboratory, investigating protein structure for his PhD.

Biological research in the late 1940s was moving in several different directions, but making little progress. A central, unsolved problem was how genetic information is transmitted from an organism to its offspring. There was little awareness in the community at large that this problem could be attacked at the molecular level, and most scientists thought that genes were proteins. In the mid-1940s, Oswald Avery and colleagues had presented evidence that DNA might be the hereditary material, but that conclusion was not widely accepted. What was needed was a catalytic event.

BETTMANN/CORBIS

That event was the arrival of Jim Watson at Cambridge in 1951. Crick was then 35 years old and Watson 23, but both shared a passion for understanding the molecular basis of genetics. They were convinced that DNA was the genetic material.

What happened next is widely known. Crick's familiarity with the X-ray diffraction patterns produced by helical structures, the access to DNA diffraction patterns taken by Rosalind Franklin, and Watson's intuitive attempts to pair nucleotide bases, facilitated by Jerry Donohue's critical intervention regarding their correct structure, led to the double-helical model of DNA in an astonishing few weeks. Their method, largely adopted from Linus Pauling, involved using accurate metal skeletal atoms to assemble a double helix, with its component chains running in opposite directions and joined by complementary base pairs in the centre. The complementarity of the two strands in the structure provided a mechanism for inheritance, in that each single strand could act as a template for assembling its complement — leading to two identical duplex molecules. The information is in the sequence of the bases. The significance of this work was not widely recognized at first, but after a few years the steady accumulation of new evidence for the double helix made it apparent that this was a

Watson and Crick in 1953.

A. BARRINGTON BROWN/SPL

transforming milestone in the development of biological science.

The next question was: how could the information housed in DNA be used to produce proteins, which do the work of the cell? Many thought that RNA played a role, but nothing was known of its structure, let alone its function. How could a nucleic acid such as RNA determine the specific sequence of amino acids that makes up a protein? This was called the coding problem, but it is interesting that many biologists at the time were largely unaware that there even was a problem.

Naive early attempts were made by Crick, Watson, Leslie Orgel and myself to formulate RNA foldings that might have specific amino-acid-binding pockets. The first published proposal for a solution, however, was by George Gamow, a colourful and highly talented theoretical physicist. Gamow playfully took the lead in forming the 'RNA Tie Club', with 20 members, one for each naturally occurring amino acid, and four honorary members, one for each nucleotide base. In addition to having a striking tie, members sent each other monographs about how the code could be solved.

In a paper circulated in the mid-1950s, Crick pointed out that nucleic acids seem to associate naturally with other nucleic acids. Thus he proposed that there might be 20 classes of 'adaptor' RNA molecules, which could line up along a template nucleic acid and each bind to a specific amino acid. Although most people were sceptical, such molecules, now called transfer RNAs, were soon discovered by Mahlon Hoagland and Paul Zamecnik. Thus, by logical deduction and intuition, Crick uncovered a key link between the RNA copy of DNA (messenger RNA) and the amino acids in protein synthesis.

In 1955, Crick invited me to the Cavendish to work on RNA fibres, and to stay with him and his artist wife Odile at their house in Portugal Place. They enjoyed hosting parties in their third-floor sitting room; the atmosphere at such gatherings was lively, with many jokes and good humour. Doing science in the mid-1950s was fun, with few worries about funding, and the exciting prospect of new discoveries on all sides.

Indeed, my short visit there extended to more than six months, because a newly arrived issue of *Nature* reported a novel form of an amino acid polymer, polyglycine II. We decided to try to solve its structure using molecular models. After only four hours of work, the coiled structure we built predicted the intensity and spacing of the published X-ray diagram. Crick suggested that we might try to write this up quickly and see if we could get it published in the next week's *Nature*. But then he paused, because he thought that the authors might feel badly, so we invited them over to look at the structure. It was characteristic of Crick that he was sensitive to people's feelings and would not intentionally cause them distress.

We later recognized that if we took three hydrogen-bonded strands from the polyglycine lattice, we could twist them slightly to make a coiled-coil structure, which was a model for collagen — the long fibrous protein of skin. Optical diffraction studies demonstrated that it was the correct structure.

This close collaboration made me appreciate the force of Crick's intellectual drive and the subtlety of his thinking. Our research progressed through an endless dialogue, looking at many sides of the problem. Crick had a strong competitive approach to science — other groups were working on collagen. But his basic attitude was not ego-driven; it had deeper roots. Like Pauling, my postdoctoral mentor, Crick was motivated to show that living systems could be explained by chemistry and physics, thereby supporting his world view as an atheist.

There remained the problem of determining the number of nucleotide bases that are needed to specify one amino acid for protein synthesis. This problem was solved in 1961 by Crick and Sydney Brenner, a collaborator of Crick's for many years. In a microbial experiment, a mutagen was used that added nucleotides. Adding one or two nucleotides blocked protein synthesis, but after three nucleotide bases were added, protein synthesis resumed. This simple but elegant experiment showed that the genetic code involves triplets of bases.

Certain inconsistencies arose in interpreting the interactions between the triplet of bases that defines an amino acid in messenger RNA and the triplet of bases in the transfer RNA molecule. To account for that, in 1966 Crick proposed the 'wobble' hypothesis, in which one base of a transfer RNA could adopt two different positions, hydrogen bonding in two different ways. This led to the complete genetic code, relating each amino acid to one or more nucleotide triplets. These monumental discoveries provided the basic framework for understanding the flow of information, and defined the major features of all living systems at the molecular level.

In 1977, Francis moved to the Salk Institute in La Jolla, California, home of his long-time collaborator Orgel. The move was associated with a shift in his interests away from problems of molecular biology and towards brain mechanisms — more specifically, consciousness. I stayed in touch with Francis continuously, and in our last conversation, about a week before his death, he said he was feeling much the same and working hard on a manuscript that he hoped to publish. His concern at the time was that the paper was too long, and that the journal might want it to be considerably reduced.

Alexander Rich is in the Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139-4307, USA.

Charles F. Stevens continues:
A week before Crick died, Terry Sejnowski and I went to see him at home to talk about plans for the new Crick-Jacobs Center for Computational and Theoretical Biology at the Salk Institute. We found him, surrounded by papers, sitting in a chair next to a window that looked out over his patio. He looked much the same as usual, dressed in slacks, a shirt open at the neck, a sports jacket. But a walking stick leaned against his chair, and his ankles were swollen.

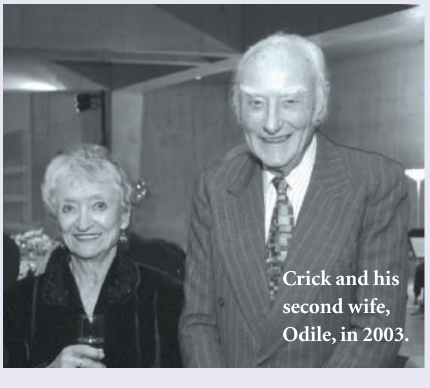
We talked for about an hour, most of the time about his new passion, the claustrum. Crick was writing a review article on this obscure brain nucleus, and he had sent me a rough draft the week before to get my comments. What had fascinated Crick was that the claustrum gets its input from many cortical areas in the brain, and sends its output back to those areas.

This arrangement made him think that perhaps the claustrum was a sort of conductor of the cortical 'orchestra'. He had a strong hunch, based on its connection pattern, that the claustrum might be a neural structure central to consciousness — we argued for a while about the likelihood of this possibility — and he said he hoped his article would stimulate research on a neglected brain area that he cared about. As we were leaving, Crick faltered briefly as he got up from his chair, and then said, with a characteristic twinkle in his eye as we shook hands, "I can still manage to stand up to say goodbye". He had had colon cancer for several years. His chemotherapy was no longer working, and he had said, quite dispassionately, that it was unlikely he would live through September. As ever, he was passionate about his science and unsentimental about what he could not control.

Many things in this last meeting were characteristic of Crick. Just as the secret of heredity lay in a structure, so did he seek gold once more — consciousness, this time — in brain structure. He always sorted through problems to find those that could be formulated as crisp questions, just as now he defined what properties he thought brain structures involved in consciousness should have, and then browsed through possibilities to find answers. And he was really interested in qualia — how subjective feelings arise — but settled for a question that he thought could be answered, what neural structures and activities are required for consciousness. He had the idea that, in getting any answer, this might, if you're clever enough and lucky enough, give you insights that will help with the harder question you really want to answer.


M. LIEBERMAN/SALK INST.

Crick with Christof Koch in March this year.


M. LIEBERMAN/SALK INST.

Crick and his second wife, Odile, in 2003.

Crick was a theorist rather than an experimentalist, and he believed strongly that theory is necessary in biology not only to organize and explain phenomena, but also to define the questions that need to be answered. After defining such questions, he then stimulated (sometimes nagged) experimentalists to answer them. Although he was devoted to theory, generally his theoretical notions were not especially quantitative. Rather, he sought to abstract the essential and very simple mechanisms from the detail.

After he moved from Cambridge to the Salk a quarter of a century ago, Crick used to invite neurobiologists to spend time with him. I made the pilgrimage about 20 years ago, before I moved there, and we spent a week talking about the visual system and the hippocampus — all day, every day, and sometimes into the evening. But Crick found certain people especially congenial for his give-and-take, and formed long-lasting and close collaborations that were particularly important to him. In neuroscience, first Graeme Mitchison and then, for the past 15 years, Christof Koch were his main collaborators. Koch regularly worked with him on ideas about consciousness, and Crick depended on these interchanges for formulating his programme to identify what they always called the NCC (the neural correlates of consciousness). And the give-and-take with Koch was terribly important emotionally as well as intellectually.

Francis stimulated many neurobiologists, myself included, by his keen questions about their work and his sharp insights. But his contributions to neurobiology vanish in comparison with what he did in molecular biology. Possibly his most influential contribution to neurobiology was making the study of consciousness respectable. Francis said, famously, about his work with Watson that, "It's true that by blundering about, we stumbled on gold, but the fact remains that we were looking for gold". Perhaps, had he been 20 or 30 years younger when he started in neurobiology, he might have found gold in the study of consciousness, too.

Charles F. Stevens is in the Molecular Neurobiology Laboratory, Salk Institute, 10010 North Torrey Pines Road, La Jolla, California 92037, USA.
e-mail: stevens@salk.edu