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Francis Harry Compton Crick OM. 8 June 1916 −− 28 July 2004

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Elected FRS 1959

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The first half of the twentieth century saw a profound change in our understanding of the chemistry underlying biology. We came to learn in detail how the small molecules upon which life is based are interconverted by specific enzymes, a web which increased in complexity and became modern biochemistry. Intellectually, a quite separate development—molecular biology—arose from physicists and chemists studying the structure of proteins with X-rays, and biologists studying viruses that infect bacteria. Its intellectual thrust was to discover how information in genes is expressed and controlled. This led to a revolution in our understanding of biology, and no person was more influential in shaping and guiding this emerging field than Francis Crick.

EARLY LIFE

Francis Harry Compton Crick was born on 8 June 1916 to Annie and Harry Crick in the village of Weston Favell, near Northampton. The Cricks were quite well-off, having inherited a share of a once prosperous shoe and boot manufacturing business in Northampton that included several retail shops in London. Annie Wilkins' family, from Northampton, owned a chain of clothing shops of which she and her sister, Ethel, inherited one. Aunt Ethel came to admire her nephew Francis and subsequently helped him financially. Anthony, Francis's younger brother, qualified in medicine and later emigrated to New Zealand.

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Figure 1. Francis, aged 5. (Courtesy of the Crick family.)

As a child (figure 1), Francis was curious about the world around him. He was stimulated by Arthur Mee's *Children's Encyclopedia*, which he devoured avidly and began to worry that by the time he had grown up, everything would have been discovered. Although Francis's family background was steeped in business, his grandfather, Walter Drawbridge Crick, had been an enthusiastic naturalist who had assimilated *On the origin of species* by Charles Darwin FRS; he discovered two new fossil gastropods, which were named after him. Later, he corresponded with Charles Darwin about a tiny mollusc which he found attached to a water beetle, an association that might provide a piggy-back mechanism for dispersal.

Francis started his education at Northampton Grammar School, moving to Mill Hill School in London as a boarder in 1925, where he had gained a scholarship. He flourished there, specializing in physics, chemistry and mathematics. His contemporaries at Mill Hill remember him as a witty prankster, full of fun and cunning. For example, it was strictly forbidden to listen to the radio during evening prep hours; teachers patrolled the study corridors in search of violations. Francis wired up his home-made radio so that when the study door was opened, the electrical circuit would break and the radio turn off. One day the teacher entered the study and shut the door behind him, remaining within. The radio did not restart—Francis had foreseen this possibility and inserted a manual control in his desk. During the school holidays, he made explosive devices—bottle bombs, glass bottles stuffed with explosives—which he ignited by remote control in his uncle Walter's garden, or he played tennis with Anthony. However, he failed to pass the entrance examinations at Oxford or Cambridge, probably because of his lack of interest in learning the dead language, Latin, a requirement until around 1961.

Francis joined University College London to study physics in 1934; with lectures less than stimulating, he took up horse riding and led an active social life. His circle included Ruth Dodd, a student of English literature, whom he married in 1940 and with whom he had a son, Michael (figure 2). His three years as an undergraduate ended with a good class II degree in 1937. Taking the path of least resistance, he remained at UCL to study for a PhD (figure 3); the topic—how the viscosity of water changes at temperatures above $100°C$—was given to him by Professor Edward da Costa Andrade FRS. Two years were spent building a high-pressure

Figure 2. Francis with his son Michael, about 1943. (Courtesy of the Crick family.)

apparatus in which water's viscosity could be measured by the damping of an oscillator set in motion by an electronic circuit. This tedious project, 'the dullest problem imaginable' as he later described it, was initially interrupted by the outbreak of war and finally by a parachute landmine which fell on UCL.

WAR YEARS

Francis was appointed, as a civilian, to work at the Admiralty Research Laboratory at Teddington, West London, in a group led by Harrie Massey (FRS 1940). Their objectives were to find ways of neutralizing German magnetic mines and mine sweepers. Thus, as German submarines emerging from a French port were usually preceded by a minesweeper, the group devised a mine with a circuit which detected the strong magnetic field of the minesweeper as it passed over, after which a much more sensitive system was activated to detect and destroy the following submarine. Later, Germany developed the *Sperrbrecher*, a particularly effective minesweeper with a huge electromagnet suspended far ahead of the sweeper. Here, the trick was to make the detection device so insensitive that it only responded when the *Sperrbrecher* itself was directly above it. In all this, Crick's ingenuity and knowledge of physics, particularly electric circuitry and hydrodynamics, were at play—an echo from his past youthful japes. After the war, he was transferred to the intelligence section and initially applied for a permanent post. However, he then decided to leave the Admiralty and change his direction radically. Among his colleagues, he had gained a reputation as a clear and incisive thinker; within the military he was seen as impatient, arrogant and insubordinate. But he learned how administrators think and how to handle them, an invaluable skill.

Figure 3. Francis at UCL in 1938. (Photograph by Elizabeth Vick, courtesy of MSB.)

On the personal side, Francis and Ruth had divorced; his mother, Annie, stepped in to care for Michael. Francis first met Odile Speed, a WREN (a member of the Women's Royal Naval Service) in the intelligence section, after she had spilled a bag of brussels sprouts on the floor of the Admiralty. Ever a gentleman, Francis helped her gather them up, thereby starting a life-long relationship. A vivacious character, Odile was artistic and fluent in both French and German—quite ignorant of scientific matters: in many ways so unlike, and yet complementary to, Francis. They married in 1949 (figure 4).

With the end of the war, Francis found himself at a loose end, uncertain what to do with the rest of his life. Having read many popular scientific articles, covering physics, chemistry and biology, he decided that his lack of expertise might be an advantage—he had a free choice and an open mind. One day he noticed that he was telling others about penicillin and antibiotics, of which he actually knew rather little. He realized that people chat about what they find interesting—the 'gossip test'. Applying this to his recent conversations, he narrowed his interests to the borderline between the living and non-living, and the brain. Each contained a mystery—what is life and what is consciousness? His knowledge of chemistry helped him

Figure 4. Francis and Odile at their wedding, 1949. (Courtesy of the Crick family.)

choose the boundary between the living and non-living: he had read the little book by Erwin Schrödinger (ForMemRS 1949) *What is life?* (Schrödinger 1945), which suggested to him that great discoveries were 'just around the corner'. Taking the advice of Edward Mellanby FRS, the Secretary of the Medical Research Council (MRC), he went to Cambridge and joined the Strangeways Laboratory in late 1947 to work with Arthur Hughes measuring the viscosity of a cell's cytoplasm. Their experimental system used cultured chick fibroblasts that had taken up magnetic particles to observe how these particles behave in applied magnetic fields. Their conclusions, in his first publication, were that the cytoplasm is rather like '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"' (1)*. At the end of two years, Francis reported back to Mellanby, discovering that the MRC had just decided to establish a new unit in the Cavendish Laboratory, headed by Max Perutz (FRS 1954), to study the structure of proteins using X-rays. Francis made his way there to join Perutz, John Kendrew (FRS 1960) and Hugh Huxley (FRS 1960) as a graduate student attached to Gonville and Caius College in June 1949.

Protein structure

The MRC's Unit for the Study of the Structure of Biological Systems was a small group in the Cavendish Laboratory. The professor, Sir Lawrence Bragg FRS, had pioneered the use of X-rays for elucidating the structures of small molecules. Hoping that ever larger molecules might be solved using his method, he nurtured the small group under Perutz, housed in a

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* Numbers in this form refer to the bibliography at the end of the text.

few rooms in the Austin Wing. Short of biochemical space, Perutz and Kendrew borrowed bench space in the nearby Colloid Science Department and Molteno Institute. At that time and within a short stroll, Fred Sanger (FRS 1954) was developing methods to determine the amino acid sequence of the protein insulin in an MRC group within the Biochemistry department, and Alexander Todd FRS and Daniel Brown (FRS 1982) were synthesizing nucleotides and related molecules in the Chemistry department.

Originally fascinated by its red colour, Perutz's aim was to solve the three-dimensional structure of haemoglobin, an $\alpha_2\beta_2$ tetramer having a molecular weight (MW) of around 64 000. Kendrew was similarly working on the smaller myoglobin, composed of a single globin chain. In his first year in the Cavendish, Francis tried to find a still smaller protein whose structure might be solved more readily than haemoglobin or myoglobin. He tried to purify several candidates, his greatest success being with the tiny pancreatic trypsin inhibitor (MW 6500); however, the crystals were too small. Crystals of the related soybean inhibitor, provided by Moses Kunitz of the Rockefeller University, contained 60 molecules in the crystallographic unit cell, too large to be useful. At the same time, he was learning the theory and practice of crystallography. In a local seminar, he suggested that the only way to determine the structure of a large protein like haemoglobin would require using the method of isomorphous replacement, a way to solve the 'phase' problem, which had earlier been used for small molecules. To Bragg, who had been overseeing Perutz's efforts, this gratuitous advice from a novice in crystallography was infuriating. However, the suggestion did point to a way forward and, over time, has proved to be correct.

It was well known that identical chemical units strung along in a linear molecule will adopt a helical conformation. How this might apply to the backbone of a polypeptide chain was explored by Bragg, Kendrew and Perutz in 1950 by model building. They failed to come to any clear conclusions about which structures were plausible (Bragg *et al.* 1950). However, the following year and using the same approach, Linus Pauling ForMemRS, R. B. Corey and H. R. Branson of Caltech discovered a motif commonly found in proteins—the α-helix, with a pitch of 5.4 Å and 3.6 residues per turn (Pauling *et al.* 1951). In failing to discover the α-helix, Bragg and colleagues had made two errors: their peptide bonds were not planar and they assumed that there should be an integral number of residues in each repeat along the screw axis. That he had allowed Pauling to beat him to the α-helix was, for Bragg, 'the biggest mistake of my scientific career'.

The following year Bill Cochran (FRS 1962), Vladimir Vand and Francis deduced the X-ray diffraction pattern generated by a helical molecule (2), in an important paper which was greatly to improve Francis's standing in his relationship with Bragg. He and Cochran then applied this theory to calculate the diffraction pattern expected from oriented fibres of poly-methyl-glutamate, a synthetic polypeptide, assuming that the backbone had an α-helical conformation (3). The predicted pattern, with a 5.4 Å helical pitch, agreed very well with that found experimentally by a group at the Courtaulds Research Laboratories. From this, Francis realized that, with an accurate model of a helical polymer, one could deduce much about its diffraction pattern, and vice versa. A year later he showed that, if α-helices are slightly deformed, the 'knobs' of the projecting side chains on one helix can more easily find a hole in an adjacent helix. In this way, helices can pack together more tightly to form a coiled-coil with a pitch of 5.1 Å. In the case of α-keratin, the protein which provides skin with its durability, such a packing of helices explains the observed strong meridional 5.1 Å reflection (4).

Figure 5. Francis and Jim in the Cavendish, 1953. (Photograph by Anthony Barrington Brown, copyright Gonville and Caius College, Cambridge.)

THE DOUBLE HELIX

The year 1951 saw the arrival of James (Jim) Watson (ForMemRS 1981) (figure 5) in the Unit, which would have profound consequences for all. Jim's passion was genes and what they are; this grew out of his background in the genetics of bacteria and the viruses which infect them (usually called 'phage') and was fired by reading Schrödinger's book. This youthful American, aged just 23, and Francis—now 35—formed an immediate friendship: they were deeply interested in similar problems in biology and impatient with conventional wisdom. Jim's arrival also brought scientific connections to the 'Phage Group', an avant-garde group of American biologists formed around Max Delbruck (ForMemRS 1967; of Caltech); they included Salvador Luria (of Urbana, Illinois), Alfred Hershey (of St Louis, Missouri), Seymour Benzer (ForMemRS 1976, of Purdue, Indiana) and Renato Dulbecco (ForMemRS 1974; of Caltech).

That the genetic material is DNA had been established, although not universally accepted, by the painstaking work of Oswald Avery ForMemRS 1944 and his group at the Rockefeller Institute in New York in the 1940s (Avery *et al.* 1944). They showed that highly purified DNA from one strain of pneumococcus could permanently transform a different strain. Later, Hershey and Martha Chase came to the same conclusion: they demonstrated that, when a phage T2 infects *Escherichia coli*, the majority of its DNA is injected into the bacterium whilst the phage proteins remain on the surface. Furthermore, a substantial portion of the DNA is found in its progeny, whilst none of the protein is (Hershey & Chase 1952).

The chemistry of nucleic acids had been well established by the early twentieth century, largely by Phoebus Levene at the Rockefeller Institute in New York. These molecules fall

into two classes based on their sugar content: either ribose (in ribonucleic acid, RNA) or deoxyribose (deoxyribonucleic acid, DNA). Both are polymers having an alternating sugar–phosphate backbone with a nitrogenous base attached to each sugar. There are four different bases: two purines, adenine (A) and guanine (G), and two pyrimidines, cytosine (C) and thymine (T) (or the closely related uracil (U) in RNA). Levene left an unsubstantiated suggestion that the bases A, T, G and C in DNA existed in a repeating tetranucleotide sequence, an idea which persisted. Pure preparations of DNA are highly viscous, allowing fibres to be pulled from concentrated solutions. In an X-ray beam, these fibres give a diffuse X-ray diffraction pattern, first obtained by Florence Bell and William Astbury (FRS 1940) at Leeds University in 1938. They found a strong reflection along the fibre axis at 3.3 Å which, they concluded, corresponds to 'a close succession of flat or flattish nucleotides standing out perpendicularly to the long axis of the molecule to form a relatively rigid structure' (Astbury & Bell 1938). Later, Maurice Wilkins (FRS 1959) and then Rosalind Franklin, in an MRC unit in King's College London under the guidance of John Randall FRS, continued to obtain ever higher quality X-ray diffraction patterns.

In November 1951 Jim attended a seminar by Franklin at King's College in which she showed striking X-ray pictures of fibres of DNA, together with conclusions about the size of the unit cell and its water content. Based on what Jim could remember of the talk, he and Francis hastened to build a helical structure for DNA. Because of its low water content and high density, they conjured up a cylindrical structure containing three chains wound around each other and held together by salt linkages in its interior. This untidy structure placed the bases projecting outwards from the cylinder. With a beginners' enthusiasm for having solved a grand problem, they invited several guests, among them Franklin and Wilkins from London, to view it. It transpired that their model had been based on false assumptions about its water content—owing to Jim's lack of attention at the seminar—and, with much embarrassment, was abandoned. This public fiasco led Bragg to forbid the duo from pursuing the DNA structure. In early 1952, Pauling and Corey published a helical structure for DNA (Pauling & Corey 1953), based on the early X-ray pictures published by Astbury and Bell. It also contained three strands and also placed the bases sticking outwards from the helical axis. This structure was also clearly wrong, depending as it did on a protonated phosphate backbone (the pK_a of the phosphate is below 2). As Bragg now became anxious that his rival Pauling should not succeed on both the protein α-helix *and* the structure of DNA, he withdrew his earlier diktat.

An MRC report on Randall's Unit was sent to Perutz, as the head of a sister MRC unit, in early February 1953. This contained an account of Franklin's progress: she had shown that wet DNA fibres give a rather diffuse X-ray pattern, the B form, whilst drying the fibres provided a sharper picture of a more compact A form having C2 symmetry. This report, which contained numerical data of the spacings observed in the X-ray diffraction patterns of the two forms, was shown to the duo by Perutz. As this report contained information used to build the correct structure, the propriety of this act has been questioned; Perutz later defended his action (Perutz *et al.* 1969) by pointing out that the report contained only numerical data that had been presented earlier in public seminars. The features of Franklin's data which were important for constructing the model included:

1. The C2 symmetry of the A form: this is an uncommon form of symmetry which Francis understood well because it was shared by haemoglobin crystals. He realized

that this meant that there are probably just two DNA chains in each structure and that they run in opposite directions, with pseudo dyad axes perpendicular to the helical axis. Franklin also included the dimensions of the unit cell, indicating that the width of a helix is about 20 Å.

2. The presence of a strong layer line along the fibre axis at 34 Å in the B form, showing that there are 10 bases along the helix (the 3.4 Å reflection seen by Astbury and Bell × 10). Following from this—and important for model building—there is a 36° rotation screw (360°/10) along the helical axis from one nucleotide unit to the next.

Jim apparently did not understand these arguments. Whilst Francis wrote his thesis, Jim tried to build the backbone of a single strand that would form one half of a double helix having parallel chains, with a screw of 18°. Jim's model failed as there was simply too little space to fit all the atoms in. However, his structure was seen by Jerry Donohue, an American chemist who had gained his PhD with Pauling, and who shared an office in the Unit with the duo. Donohue pointed out that the chemical structures of the bases C, T and G, as portrayed in textbooks, were probably wrong: they were not enols but ketones. This radically changed their hydrogen-bonding possibilities.

Francis had learned from the α-helix debacle that model building must be accurate: he set about trying to build a backbone with a 36° screw. That done, the bases had to be fitted inside the helix. On the last day of February 1953, Jim was trying to see how pairs of bases might fit together inside the backbone, using cardboard models of the keto forms. He discovered that the overall shapes of a hydrogen-bonded AT pair and that of a GC pair are the same. These pairs fitted inside the model helical backbone which Francis had built. Francis then saw that Jim's base pairs implied that there is a dyad axis (perpendicular to the helical axis) and that this meant that the chains are anti-parallel. In other words, for Francis, the anti-parallel nature of the double helix, deduced from the C2 symmetry, was confirmed by the shape of the base pairs that Jim had found.

Once a model having two co-axial chains of opposite polarity and with fitting base pairs had been built, a stream of visitors came to view it: these included Bragg, Wilkins, Franklin, Dorothy Hodgkin FRS, Brown, Todd, Pauling and Sydney Brenner (FRS 1965). An extraordinary paper was written and, graced by an outline model of a double helix drawn by Francis's wife Odile (figure 6), appeared in *Nature* on 25 April 1953 (5). This was accompanied by two papers from the King's MRC unit reporting the X-ray results of Wilkins, A. R. Stokes and H. R. Wilson (Wilkins *et al.* 1953) and of Franklin and Raymond Gosling (Franklin & Gosling 1953).

Base-pairing, as soon as Jim discovered it, provided an immediate answer to a problem which many thinkers, such as Schrödinger, had pondered. How can genetic information be copied and multiplied? The genetic implications of the structure were published in a second paper in *Nature* at the end of May 1953, where the answer to this enigma—that each separated strand of DNA contains a full complement of the genetic information which can be copied by base-pairing—is spelled out (6).

Their model also provided a basis for some of the reported properties of DNA. Titrimetric studies of DNA solutions by John Masson Gulland FRS (of Nottingham) in 1947 had shown that the amino and enol groups of the bases in DNA are initially inaccessible to both acid and alkali, but at some stage the structure collapses, allowing these groups to become ionized; back titration is thereafter normal. To explain this observation, he had suggested that the

This figure is purely
diagrammatic. The two
ribbons symbolize the
two phosphate—sugar
chains, and the hori-
zontal rods the pairs of
bases holding the chains
together. The vertical
line marks the fibre axis

Figure 6. The double helix, drawn by Odile, 1953. (Copyright *Nature*: reproduced with permission.)

bases are hydrogen-bonded within a structure which is sensitive to both pH extremes; in either case, the viscosity of the DNA solution falls when the structure is impaired (Gulland *et al.* 1947). Between 1951 and 1952, Erwin Chargaff of Columbia, NY, had measured the base compositions of DNA from different tissues and creatures. He found that different species may have different base compositions, but that each contained equimolar amounts of purines and of pyrimidines, with approximate molar equivalences of As and Ts, and of Gs and Cs (Chargaff *et al.* 1952). The proposed DNA structure implied that these ratios are exactly 1.

The impact of the Watson–Crick model, among the few who shared their enthusiasm for the problem, was profound; outside that group, it went largely unnoticed. In the following years, Wilkins obtained increasingly improved X-ray diffraction patterns. In 1958, Matthew Meselson and Frank Stahl at Caltech showed that, during replication, the two strands of DNA separate and each gives rise to a daughter double helix (Meselson & Stahl 1958). In 1961, John Josse, Dale Kaiser and Arthur Kornberg (ForMemRS 1970) at Stanford measured the frequency of next-door neighbours between nucleotides in DNA. The patterns they found showed that the expected base pairs exist and that in the double helix the two strands have opposite polarities (Josse *et al.* 1961).

In 1968, Jim published a personal account of the discovery in the *The double helix*, which became a best seller (Watson 1968). The breakthrough is also described in *Life story*, a BBC film (with Tim Pigott-Smith as Francis, Jeff Goldblum as Jim, Juliet Stevenson as Franklin and

Alan Howard as Wilkins), which should be shown in all schools: it is a wonderful portrayal of the nature of discovery, with much attention paid to scientific detail and accuracy, ending with the excitement of seeing that which no one has ever seen before.

Rosalind Franklin became good friends with the Cricks. Towards the end of her life she stayed with them when undergoing treatment for ovarian cancer; she died in 1958.

Virus and polyA structure

At the border between the living and non-living are the viruses. At that time, only plant viruses had been analysed: they contained just protein and RNA. Jim had been interested in the best known, the rod-shaped tobacco mosaic virus (TMV), studying it with X-rays and finding that it has a helical construction. Building on this, Francis and Jim suggested in 1956 that the role of the protein component of viruses is to form a cover, or shell, to protect the genetic material. In TMV, this is achieved by forming a rod in which identical protein subunits bind along the RNA molecule, so covering it; as each protein unit makes the same chemical interactions with its neighbour, the stack of them forms the observed helix. They extended these ideas to spherical viruses, where the RNA would be packed inside a protein coat. Two such viruses (bushy stunt virus and turnip yellow mosaic virus) had been shown to form crystals in which the unit cell is cubic. They argued, from symmetry considerations, that the way in which identical protein subunits can pack into a shell is limited and must be composed of 12, 24 or 60 asymmetric units (7). This indeed is how small viruses are constructed.

Polyriboadenylic acid (polyA) self-associates at an acidic pH. Using polyA fibres and X-rays, Francis, Alex Rich, David Davies and Jim solved its structure. It forms a double helix in which the two chains are parallel and form the outside of the compact structure. Inside it, each adenine base forms three hydrogen bonds with its neighbour on the opposite chain (10).

On protein synthesis

As there is nothing with informational content in a double helix other than its nucleotide sequence, that was where the genetic information had to be. Sanger's pioneering methods for analysing amino acid sequences had revealed, by 1953, the complete and unique sequences of the two chains of insulin (Sanger & Thompson 1953). It therefore seemed likely that, both polypeptides and DNA being linear chemical structures, the sequence of nucleotides in DNA provides the information for the sequence of amino acids in proteins. In 1954, the cosmologist George Gamow in Washington DC proposed his 'diamond' code, in which he suggested a specific way in which the DNA could align amino acids (Gamow 1953). Although quite wrong, it helped to define the problem: the exact relationship between the base sequence of a nucleic acid and a protein sequence, noting that at least three bases are needed to specify any particular amino acid.

In 1954, Gamow and Jim formed the 'RNA Tie Club', a disparate collection of Gamow's friends who were interested in the coding problem and the role of RNA. The group was limited to 20 members (one for each amino acid; Francis was tyrosine, Jim was proline) and included Richard Feynman (ForMemRS 1965) and Edward Teller; its role was to exchange ideas between members, although communication was usually by letter and the club never met as a body.

Gamow's diamond code spurred Francis and others to think about specific coding mechanisms and to focus on how proteins might be assembled. The imponderables were many: does just one strand of the double helix code for proteins and, if so, how is the correct strand selected? Is the template nucleic acid DNA or RNA? How are individual genes demarcated? Is the code the same for bacteria and mice? How many, and which, amino acids are encoded? Francis and Jim settled on the 'standard' 20, rejecting hydroxyproline, phosphoserine and several others as being found in only a few proteins, although Francis considered that perhaps the number should be 21, allowing also for 'terminate'—where the polypeptide ended—to be encoded.

In 1957 Francis, together with John Griffiths and Leslie Orgel (FRS 1962), proposed the 'comma-less code', initially aired in a paper to the RNA Tie Club (8). Assuming that a nucleotide sequence is read in triplets, they asked whether there is a unique way of reading the sequence so that only one phase is readable (the other two phases being 'nonsense'). If the sequence ATC.GTG appears as sense in the template, then TCG and CGT must be unreadable—they have to be nonsense. This restriction reduced the number of coding units— 'codons', introduced by Francis in approving a manuscript (Bretscher & Grunberg-Manago 1962)—from 64 to just 20, the 'magic number'. As Francis would later relate, 'It was a beautiful idea which was completely wrong!'

Alongside these thoughts about the nature of the code, Francis also pondered over the nature of the flow of information from nucleic acids into proteins. Cells highly active in making proteins had been found to contain high levels of RNA, this RNA being outside the nucleus, in the cytoplasm. This is where proteins are made. This link between RNA location and protein synthesis became clearer when, in 1955, Paul Zamecnik and colleagues of the Massachusetts General Hospital in Boston showed that cytoplasmic particles—then called microsomes, now ribosomes—which contain much of the cell's RNA, are the sites of protein synthesis (Littlefield *et al.* 1955). As RNA could be transcribed from DNA using base-pairing, the emerging picture seemed to hang together: the RNA in ribosomes contained the information from genes and this would act as the template for polypeptide synthesis.

Francis's ideas were first publicly aired in a talk, 'On protein synthesis', which he gave to the Society for Experimental Biology in London at the end of September 1957, and were published in 1958 (9). Aside from the DNA articles, this was his most influential theoretical paper. It defined what we now see as the heart of modern molecular biology. The essence of this paper follows, although much more of his thinking was presented.

He first formalized what many supposed: that the information in a piece of nucleic acid is contained within the sequence of its bases and that this is translated into the sequence of amino acids in a polypeptide chain—his 'Sequence Hypothesis'. He listed the 20 amino acids which he thought are involved in this information flow. More importantly, he proposed that once the amino acids are assembled into a polypeptide chain, it is the sequence of amino acids itself which guides the polypeptide chain to fold up into its final three-dimensional structure. This defined what became known as the 'folding problem'.

On the nature of genetic information held in DNA, he proposed that information flows from DNA to DNA (during replication) or to RNA (in transcription) and then possibly back again into DNA. Information also flows from the nucleic acid sequence into a protein sequence, but *never* the other way round. Once the protein has been made, the information required can never get back into a nucleic acid. This he termed his 'Central Dogma'.

He summarized what was then known about protein synthesis, in particular that proteins are made on microsomes and that each constituent amino acid is first activated by a specific enzyme and ATP before moving to the microsome. As microsomes were known to contain much RNA, it was presumed to be the template for directing amino acid assembly. But how did an activated amino acid interact with the template so that it, and not some other, was incorporated into the polypeptide? If an amino acid is encoded by, say, AGC, how can that amino acid recognize this triplet? Francis suggested that the differences between amino acids lies in their side chains—some have a variety of hydrophobic shapes, others have ionized groups. These features are best distinguished by proteins. On the other hand, the template nucleic acid, whether DNA or RNA, presents a hydrogen-bonding surface whose chemical character is to discriminate between nucleic acids and is unsuitable for differentiating between amino acid side chains. This led Francis to predict that an intermediary—an adaptor nucleic acid molecule—must exist between the two. He imagined that there are 20 different adaptors, one for each amino acid and that these are composed of a short nucleic acid. In this scheme, an enzyme would attach an amino acid to its own specific adaptor, after which the identity of the complex would reside solely in the adaptor. The adaptor would position the amino acid in its correct place on the template. He called this his 'Adaptor Hypothesis'. It reveals his astonishing insight and understanding of molecular interactions; it was first communicated to the RNA Tie Club in early 1955.

At around the same time as Francis's talk 'On protein synthesis', Mahlon Hoagland and Zamecnik discovered a transient cytoplasmic intermediate in protein synthesis, an amino acid–RNA complex (Hoagland *et al.* 1958). Whereas Francis had imagined that the adaptors would be a few nucleotides long, these 'soluble RNA'—now called 'transfer RNA'—molecules are about 80 nucleotides long. During protein synthesis, their role is more complex than just as adaptors; having a complex three-dimensional structure and often adorned with aliphatic side chains, they were later described by Francis as Nature's attempt to make a protein out of a nucleic acid.

In 1959, Francis was elected to the Fellowship of the Royal Society; he later referred to this honour as that which gave him the greatest pleasure.

GENES AND MUTANTS

A trickle of information was coming from the nature of mutations and their effects. In 1949, Pauling and his colleagues found that the haemoglobin in sickle cell disease possesses an altered electrophoretic mobility. In 1957, Vernon Ingram (FRS 1970), in the Cambridge MRC Unit, pinned this difference to a single amino acid exchange of a glutamate for an alanine in the β-chain. The observation that mutations usually affect only a single amino acid suggested that the code is non-overlapping (that is, no nucleotide is shared by adjacent codons); in addition, a relationship between codons and amino acids was beginning to emerge—for example, codons for glutamate and alanine might be related by a single base change.

Mutations arise spontaneously—rare events, triggered by radiation or a range of chemicals. The rate of mutant production can be accelerated greatly by the presence of mutagens: 'nasty' chemicals (usually carcinogens), such as ethyl-methane sulfonate, bromouracil (BU), methyl nitroso-guanidine and the acridine dye proflavin (PF). It was imagined that mutagens somehow interfere with DNA replication, causing the enzymes responsible for this complex

copying process to insert the wrong base into the new DNA strand. Mutants can usually be reverted to the wild type by a mutagen; such reversions often occur at, or near, the same genetic site as the original mutation, suggesting that the original flaw is being corrected (Benzer 1961).

Sydney Brenner joined the Unit in 1957. With Benzer as a sabbatical visitor, they generated a collection of PF mutants in the phage r_{II} region. They found that the sites at which mutants are induced by BU are in strikingly different locations along the gene from those induced by PF. Further, Sydney Brenner and Alice Orgel showed that mutants induced by PF and those induced by BU fall into two separate classes: those induced by BU cannot be reverted by PF, and vice versa. This led Sydney and Francis, with Leslie Barnett and Alice Orgel, to put forward 'The theory of mutagenesis' (11) in early 1961. They proposed that there exist two classes of chemical mutagen: (1) those which lead to the exchange of one base for another, the 'base analogue' mutagens (such as BU); and (2) those which effect the insertion (or removal) of a base in the DNA, the acridine mutagens (such as PF). In the latter case, they suggested that an extra base in the template would, during protein synthesis, change the reading phase in the template so that a nonsensical polypeptide was produced after that site. Further subtraction of a base, either upstream or downstream of the original insertion, would restore the correct phase (but leave the protein with a new sequence between the two sites). In this way, the original mutation could be reverted. That acridine mutagens might lead to the insertion of a base in the DNA fitted with the observation of Leonard Lerman that acridine dyes bind to DNA by intercalating between the bases (so that the double helix is lengthened) (Lerman 1961).

Francis decided to study the collection of acridine mutants isolated by Benzer and Sydney. He found that these mutants could be assigned to one of two classes, which he arbitrarily called '+' and '−'. Most + mutants, when combined with any −, yielded the wild-type function. This fitted with their new interpretation of how PF acts. There were a few combinations which did not work and these were set aside; later these 'barriers' were found to be phase-sensitive termination codons.

On holiday in Morocco that summer, Francis realized that, if their theory was correct and if the code was a triplet code, then any $+++$ or $---$ combination should yield a wild type. This thought ruined his remaining holiday; he returned to Cambridge to find out whether it was correct. On 17 October 1961, he had constructed his first triple $+++$, which turned out to be wild type: he recorded '∴ the coding ratio is 3' (figure 7). He set about making many more combinations (such as $++-$, which had a mutant phenotype) but found that $+++$ and $---$ generally gave a wild type (providing no barriers exist within the region). In the last issue of *Nature* in 1961, one of the most profound papers in genetics appeared: 'General nature of the genetic code for proteins' by Francis, Leslie Barnett, Sydney and Richard Watts-Tobin (12). Besides showing that the genetic code is read in triplets (or less likely sextuplets), it also indicated that the information encoded in a gene is read from one end of the gene to the other. Because extensive regions of out-of-phase DNA could be read as something meaningful, it suggested that most nucleotide sequences code for amino acids of one kind or another. There must be few 'nonsense' sequences and this implied that the code is highly 'degenerate'. Francis's experimental work on the acridine mutants was his longest sustained laboratory work in biology.

Until February 1962, the Unit's accommodation had been primitive: a few rooms in the Austin Wing of the Cavendish Laboratory, a temporary hut ('The Hut') (figure 8), a separate room with a lean-to conservatory where glassware was cleaned ('The Greenhouse') and a

Figure 7. Experimental notes, 17 October 1961. Published with permission of the Crick family. Deposited by MSB in the Churchill College Archives.

Figure 8. 'The Hut', 1961. The front door is on the left, next to a bicycle. (Courtesy of Hans Boye.)
(Online version in colour.)

Figure 9. LMB, 1962. The emergency staircase, seen on the right, was replaced with a helical staircase
in 1964. (Courtesy of Hans Boye.) (Online version in colour.)

Figure 10. LMB Governing Board, 1962. From left: Hugh Huxley, John Kendrew, Max Perutz, Francis, Fred Sanger, Sydney Brenner. (Courtesy of the MRC Laboratory of Molecular Biology.)

short blocked off corridor with a bench along one side ('The Gallery', used by Francis for the acridine experiments). Then, in early 1962, the Unit moved into a large new building, the Laboratory of Molecular Biology (LMB) (figure 9), on Hills Road next to Addenbrooke's Hospital. With Perutz as Chairman, its new divisions were headed by Kendrew (Structural Studies, with Huxley, David Blow (FRS 1972) and, soon after, Aaron Klug (FRS 1969)) and Francis (Molecular Genetics, with Brenner, John Smith (FRS 1976) and Tony Stretton). Sanger, with his MRC group from the Biochemistry department of the University, joined them as head of Protein Chemistry (which included Brian Hartley (FRS 1971), Ieuan Harris, Les Smith and, soon after, Cesar Milstein (FRS 1975)) (figure 10). Later that year, the new LMB celebrated the awards of Nobel Prizes to Francis (with Jim and Wilkins, in Physiology or Medicine) and Kendrew and Perutz (in Chemistry). It seemed, in those heady days, as though the new lab was being christened with champagne.

Genetic code

Towards the end of the 1950s, the nature of ribosomes—the sites of protein synthesis—became clearer. They are made of two huge subunits (which in bacteria sediment at 30S and 50S) with a total mass of around 3×10^6 daltons. Chemically, they were known to contain about 65% RNA (the 16S and 23S RNAs in the small and large subunits), and the rest is protein. Until early 1960, the template for protein synthesis was assumed to lie in the RNA component. However, several inconvenient facts emerged:

1. Coming in just two sizes, the ribosomal RNA did not fit with the wide range of polypeptide sizes. Worse, its base composition, enriched in Gs and Cs, did not reflect that of the genome.
2. Experiments in the groups of Jacques Monod (ForMemRS 1968) and François Jacob (ForMemRS 1973) of the Institut Pasteur in Paris showed that the synthesis of a bacterial protein can occur without delay as soon as its gene is introduced into a cell. This seemed too short a time to first make a whole ribosome and then the protein it encoded. Furthermore, the synthesis of a particular protein can be switched off quickly, whereas ribosomes appeared quite stable.

This paradox was resolved, in theory, at a meeting in King's College, Cambridge, in the spring of 1960, which included Brenner, Jacob and Francis. They imagined that ribosomes are non-specific translation machines that translate genetic RNA—now called messenger RNA (mRNA)—which associates transiently with any ribosome to direct that ribosome to make a protein. This would tally with the observations of the Paris group that genes can be switched on quickly and, if the mRNA were unstable, be switched off quickly. Sydney and Francis realized that such an unstable RNA had earlier been discovered in T2 phage-infected *E. coli* by Eliot Volkin and Lazarus Astrachan in 1956 (Volkin & Astrachan 1956); this RNA had a base composition like that of the DNA of phage T2 (which initially misled these authors to believe that their RNA was a precursor of the T2 DNA of future phage genomes). The existence of mRNA in phage T4-infected bacteria was shown to be correct by Sydney, Jacob and Matthew Meselson (ForMemRS 1984) in early 1961 (Brenner *et al.* 1961).

This discovery was regarded by many, including Francis, as the most important—after the DNA double helix—in molecular biology. It placed the underlying picture of how genes function into a frame. It led to a search by biochemists for exogenous messenger RNAs, such as viral RNAs, which could be added to cell extracts to prime them for protein synthesis.

That summer, Marshall Nirenberg of the NIH in Washington DC announced a discovery by Heinrich Matthaei, a German postdoctoral visitor in his lab, that opened a direct approach to solving the code. Matthaei had added polyU—an RNA composed of repeating Us—to an *in vitro* extract prepared from *E. coli* and discovered that it directs the synthesis of a single kind of polypeptide, polyphenylalanine. This momentous discovery showed that a codon for phenylalanine is probably UUU (Nirenberg & Matthaei 1961) and precipitated a scramble to solve the genetic code by priming cell extracts with increasingly sophisticated synthetic mRNAs. Within the next year, the compositions of many codons were allocated to amino acids; mammalian extracts responded similarly, indicating the universality of the code. The popular press suddenly became interested, not just in the 'Code of Life', but in the double helix and inheritance. In this fever, Francis was in great demand: he was seen as the *eminence*

grise behind the revolution. His office, which he shared with Sydney, was almost a clearing house for incoming reprints, which he devoured, and outgoing letters offering advice. He gave many talks on the developing code and, when he did so, was seen as the arbiter of priorities, to which he gave careful attention. In these talks, he provided a new depth of understanding to the field as he explained how the emerging observations knitted together. Thus, Noboru Sueoka had shown that a strong correlation exists between the AT/GC composition of different bacterial species (it varies by a factor of 4) and the abundances of different amino acids within them (Sueoka 1961): his findings fitted the *in vitro* studies with, for example, phenylalanine abundance being strongly correlated with high AT. Similarly, a series of studies by Hans-Günther Wittman's group of the Max Plank Institute in Berlin were especially interesting (Wittmann & Wittmann-Liebold 1963). They produced mutants of TMV with nitrous acid, a mutagen which effectively converts $C \rightarrow U$, and $A \rightarrow G$. Many of the mutations were found to reside in the amino acid sequence of the coat protein and these were identified. Surprisingly, the range of mutations was highly restricted. For example, in several independent mutants the amino acid proline was sometimes converted to a serine or to a leucine, but to no other amino acid; the latter two amino acids, in other mutants, were converted to just phenylalanine. Contemporary *in vitro* studies showed that a polyUC coded for just these four amino acids! Both sets of results implied that a codon for proline was C-rich, with codons for serine and leucine being composed of Cs and Us. A review Francis wrote at the time (1963), 'The recent excitement in the coding problem' (13), captures the moment, as does his Croonian Lecture 'The genetic code' (16) and an exuberant card he sent whilst on holiday in Hawaii (figure 11). The 1966 Cold Spring Harbor Symposium on the genetic code opened with his talk 'The genetic code: yesterday, today and tomorrow' (15). At the symposium, his fiftieth birthday was celebrated with champagne on the lawns outside Blackford Hall with a memorable, but embarrassing, present from Jim: a huge cardboard box containing a female model who was almost bare.

The emerging code clearly had coherence: codons did not appear to be allocated at random to different amino acids. This led Francis to think about how codons are recognized by adaptors: is there more to it than standard base-pairing? Out of this came his 'Wobble Hypothesis' in 1966 (14): that the recognition of a codon by the adaptor anticodon is achieved by standard base-pairing in the first two bases, with less stringent pairing, or a 'wobble', in the last base of the codon. This wobble allows a G in the anticodon to pair with a codon C or U, a U in the anticodon with an A or G, and an I (hypoxanthine, a base related to G) in the anticodon with a U, C or A. This permitted fewer tRNAs to exist than one for each codon. How this limited specificity, combined with the accurate reading of codons, is achieved came much later from the X-ray structure of a complex of the ribosome, an mRNA and a tRNA in the ribosome's decoding site (Ogle *et al.* 2001). One of Francis's most visible and lasting contributions was to construct the ubiquitous square format in which the code is now presented.

Development

In the mid to late 1960s, as the golden age of molecular biology drew to a close, many adventurous molecular biologists sought new territory to conquer or set up a new institute, as did Kendrew (figure 12) (the EMBL). Brenner formed a highly ambitious plan of making the

Figure 11. Post card from Hawaii, 1964. Francis sent this joke card to the Molecular Genetics division, suggesting he had hired six attractive Hawaiian girls as technicians. Published with permission of the Crick family. Deposited by MSB in the Churchill College Archives. (Online version in colour.)

Figure 12. John Kendrew and Francis, around 1966. Typical pose of Francis engaged in discussion. (Unknown source.)

nematode *Caenorhabditis elegans* a model organism for genetics comparable to *Drosophila* (a goal that has been attained), at the same time building up a detailed knowledge of its neuroanatomy in order to map genetics onto neural function and behaviour (a goal still to be fully realized). The Molecular Genetics division in the LMB became the Cell Biology division, with Francis and Sydney as joint heads; they made several new appointments, which included John Gurdon (FRS 1971), Peter Lawrence (FRS 1983), John White (FRS 2005) and John Sulston (FRS 1986).

The new division included several groups working on developmental biology. Francis was particularly fascinated by patterns of cells, such as fingerprints, seen in many epithelia, and became absorbed in what underlying processes might generate these patterns. Based on their experiments, in which pieces of the epidermis of insects were transplanted, Michael Locke, Lawrence and others had proposed that a gradient of positional information guides the polarity and developmental fates of cells within the epidermis; this idea was generalized and formulated with particular clarity by Lewis Wolpert (FRS 1980), who also reviewed the long-standing conjecture that positional information is embodied in the concentration of a chemical morphogen. Francis tried to estimate over what distance it is reasonable to expect a chemical morphogen to establish a stable gradient. He took the time available as a few hours, about the same time it takes to establish patterns in the embryo. His estimate of about 70 cells (each with a diameter of 10 μm) agreed well with Wolpert's observation that fewer than 100 cells may be involved and was published in 1970 (17).

Later, in 1972, with Mary Munro and Lawrence, Francis studied the pattern of cells in the cuticle of the blood-sucking bug *Rhodnius*. The cuticle forms a pattern of consistently oriented ripples that can be interpreted as contours of an underlying gradient of morphogen (19). After an operation in which a piece of the insect's epidermis is rotated and then allowed to heal and secrete a fresh cuticle, a new pattern of ripples arises that reflects the disturbance of the

gradient by the operation. Computer simulations showed that a diffusion-based model gave a good fit to the data (though see Lawrence (1974) for a caveat).

With Lawrence, Francis wrote an influential review of the major contributions made to our understanding of how an animal is constructed. Based largely on the work of Antonio Garcia-Bellido (ForMemRS 1986; of Madrid) on *Drosophila* and on Lawrence's work on the milkweed bug, *Oncopeltus*, they explained and extended ideas about developmental compartments and morphogenetic gradients and discussed how selector genes might progressively define territories during development (21).

Chromosomes

Francis, like many others, was impressed by the images of polytene chromosomes seen in *Drosophila* salivary glands, structures with bands of varying sizes strung along their lengths. What did these bands and the spaces between them—the inter-bands—mean at a structural level? Francis thought an understanding of chromosome structure might illuminate how genes in higher organisms are organized and controlled, and this in turn might shed light on developmental processes. The amount of DNA in a higher cell is many times that required to specify the proteins it encodes. He proposed, in 'General model for the chromosomes of higher organisms' (18), that the DNA between bands (the 'inter-bands', about 4% of the total) codes for protein and the adjacent band controls its expression. In addition, he added that recognition of control sequences within bands would be helped if those control regions are single stranded. Francis's high expectations for this paper were quickly dashed: it was all a delusion and Francis went into a depression which lasted several months. Nevertheless, his interest in the problem provided encouragement to Roger Kornberg (ForMemRS 2009) to pursue the structure of chromosomes at the LMB, resulting in the discovery of the nucleosome.

As a colleague in the laboratory

When the LMB was formed, Francis suggested to the chairman, Perutz, that the lab should have a week-long internal meeting at which all scientific members give a short talk about what they are doing, why they are doing it and what they have discovered. 'Crick Week' was held in October 1962 in the lab lecture room; it became an annual event which has been widely imitated elsewhere. At these, and at other talks and meetings, Francis had a most helpful habit of rephrasing questions from the audience on topics ranging from crystallography to immunology. These interruptions always sharpened the question and often set it in a wider context. This behaviour, particularly at scientific meetings, unfairly gave him a reputation for arrogance.

In passing you in town, or seeing you in the lab, Francis would greet you with a cheery 'Hey Ho!' His typical day would find him working at his desk—reading, thinking and writing letters. Sometimes he wandered around to see what was going on. If he wanted to see you, he would come to your lab door, wait until you had spotted him and then ask you to pop by his office when convenient. Otherwise, if you wished to see him, he was available to anyone in the lab at all times, provided the door to his office was not closed for confidential meetings. A most convivial person, Francis exerted a profoundly beneficial influence across the whole LMB. During lunch in the lab canteen, he would join quite disparate groups sitting at small tables and discuss what they were doing or found interesting at the time. He frequently asked why some

From:

M.R.C., Laboratory of Molecular Biology, Hills Road, Cambridge.

Dr. F. H. C. Crick thanks you for your letter but regrets that he is unable to accept your kind invitation to:

send an autograph   read your manuscript
provide a photograph   deliver a lecture
cure your disease   attend a conference
be interviewed   act as chairman
talk on the radio   become an editor
appear on TV   contribute an article
speak after dinner   write a book
give a testimonial   accept an honorary degree
help you in your project

Figure 13. Dr F. H. C. Crick thanks … but regrets …, 1965. (Courtesy of the MRC Laboratory of Molecular Biology.)

line of investigation was being pursued, rather than some alternative: his suggestions—by an imaginative outsider—often provided a new approach or thought. Students and post-docs, of whom some eight went on to win a Nobel prize, learned how to approach scientific puzzles. After lunch, he might return to the divisional coffee room, next to his office, where he and Sydney would chat about anything, but usually science—a recent paper or preprint, and what it might mean in the grander scale of things. His aim was to understand the natural world around him and how it all happened. Hence his interest in the origins of life and his impatience with religion, which he regarded as a man-made obstacle.

For someone of his stature, the length of Francis's list of publications is modest. In part this reflects his views on authorship, views shared by both Jim and Sanger. For Francis, only those who had contributed to the experimental section, or who had made a substantial theoretical contribution, should be authors. In today's climate, this might be suicidal for any scientist's career; the honesty it reflects was even then uncommon. He had a surprisingly catholic view of science: he well understood that scientific opinions, even the apparently ridiculous, must be respected until shown to be wrong. Conversely, a clever solution to a vexatious problem might not be correct, as his own 'comma-less code' so neatly demonstrated.

Within the minds of scientists, there is a close association between individuals and their ideas: placing an individual on a pedestal sets him apart from his colleagues and isolates him from criticism. For this reason, Francis eschewed many honours, although he did accept an OM in 1991 (having declined a CBE in 1963). A card he used in the early 1960s—now a collector's item—expressed his regret at being unable to accept various types of 'kind invitation' (figure 13).

Overview of Francis and molecular biology

Francis's discoveries—the DNA structure, the adaptor hypothesis, the triplet nature of the code, the wobble hypothesis, for example—were each a major intellectual achievement.

What a description of his scientific achievements fails to convey is the intellectual impact he brought to all of molecular biology. Incessantly talking and listening, and then suggesting what experiments to try or what he thought might be the reality, forced his interlocutor to sharpen his thinking and look at the wider picture. This generosity he shared quite freely. Like Jim, he brought a freshness of approach and honesty that pervaded molecular biology. Competition between individuals is a natural human endeavour and is part of the fun of science. But helping to ensure that credit goes where it is due is important for civil behaviour: Francis was always careful to use his considerable influence to promote this objective. Without Francis, the edifice of molecular biology would have emerged, but in black and white. Francis helped give it excitement, integrity and colour.

It is a matter for conjecture whether solving the structure of DNA gave Francis the daring to attack molecular problems in the way he did. But he was in no doubt, as he wrote in *What mad pursuit* (1988), that 'Rather than believe that Watson and Crick made the DNA structure, I would rather stress that the structure made Watson and Crick'.

With the foundations of molecular biology in place, the stage was set for the invention of DNA cloning and other techniques; these would reveal how genes in higher organisms are organized and provide routes into the whole of biology, particularly into development, immunology and the understanding of genetic diseases. Exploiting these advances, many new drugs and improvements to medicine have been developed.

California

Francis spent a sabbatical year at the Salk Institute in 1976, and a year later moved there permanently as the J. W. Kieckhefer Distinguished Fellow (figure 14). Initially, he worked with Leslie Orgel, then resident at the Salk, on the concept of selfish DNA (23), an extension of the ideas of Richard Dawkins (FRS 2001) of the selfish gene. From around 1980 he largely put aside molecular biology to work on the brain—a bold step to switch so late in life from molecules to what goes on inside one's cranium. One might have imagined that he would look down on the new subject from on high; instead, he started at the beginning, read widely on neuroanatomy, neurophysiology and psychology and invited many experts in these fields to visit him at the Salk.

His room at the Salk had belonged to Jacob Bronowski, and commanded a superb view of the Pacific Ocean, with hang gliders passing to and fro along the cliff top. A model of the brain occupied a prominent place on a table top.

Thinking about the brain

Francis's work on the brain can be divided into two phases. In the first, he speculated about the mechanisms underlying brain function, particularly visual perception. In the second, he focused on consciousness, the remaining 'mystery' he had contemplated working on when he was a young man.

In the first phase, his aim was to spot key features of the brain's processing mechanisms, concentrating particularly on vision, which is the best studied of the senses and has the largest representation in the cortex of many mammals, including humans. One gets an impression of him rolling up his sleeves for this task in his early survey article on the subject, 'Thinking

Figure 14. Francis and Odile in California, 1999. (Courtesy of the Crick family.) (Online version in colour.)

about the brain' (22). Another manifestation of this early enthusiasm was the founding of the Helmholtz Club, a rather exclusive discussion forum for neuroscience, co-founded with V. S. Ramachandran and Gordon Shaw. The RNA Tie Club was the model, and indeed it was initially called the 'vision tie club'. However, it differed from its precursor in that its members met (rather than writing letters), and these meetings were very convivial, with plenty of wine flowing over dinner. It also had a broader remit than its precursor, which had been focused on obtaining the genetic code and had a comparatively short lifetime. The Helmholtz Club flourished for more than 20 years, and was a life-long inspiration to many who attended it.

Francis's first original neuroscientific publication is concerned with the problem of 'binding' of visual features that belong to one object (e.g. the edges that outline a face) (24). It had been proposed that the firing of neurons representing such features could be synchronized by a temporary strengthening of synapses between them (von der Malsburg 1981). Francis suggested that the synapses in question could lie on dendritic spines, short protrusions from dendrites that receive synapses from axons nearby, and that spines could change shape rapidly, thereby changing their electrical properties. The idea of rapid shape change seems to be correct

(McAlonan *et al.* 2006), though whether it occurs on the very short time scale he had envisaged or has anything to do with feature-binding is presently unknown.

Francis's next two papers were co-authored with GJM. The first was based on an observation that a pattern of stripes is produced when horseradish peroxidase is injected into the primary visual cortex of the tree shrew (Rockland & Lund 1982). They explained this pattern by positing a particular kind of long-range connection that would allow the receptive fields of neurons with similar orientation preferences to be 'stitched together' to make long receptive fields (25), a conjecture which now has strong supporting evidence (Bosking *et al.* 1997).

The second paper was on a more controversial topic: a proposal for the function of dream sleep (26). This was based on the idea that the waves of activity originating in the brainstem that characterize dream sleep (PGO waves; McCarley *et al.* 1983) can elicit patterns of neural activity in the cortex that are excessively excitable. These patterns, it was suggested, tend to impair memory function, and could be tamped down by weakening the associated synapses, using a process called 'reverse learning'. A very similar proposal was made independently for memories embodied in abstract neural nets (Hopfield *et al.* 1983). So far, there is little evidence for the dream hypothesis.

Francis then returned to a problem of visual perception: the detection of an odd-man-out in a field of features. This task (Treisman & Gelade 1980) can sometimes be done easily and rapidly, e.g. when spotting a red letter in a field of green letters. However, more complex versions of the task often require a time proportional to the number of features in the field, and this can be explained by a notional 'spotlight' moving over the field searching for the target. Francis observed that a structure called the reticular nucleus of the thalamus is ideally endowed to be the neural underpinning for this spotlight (27). The thalamus is a kind of gateway through which sensory inputs pass on their way to the cortex, and the reticular nucleus forms a thin envelope around the thalamus and has wide-ranging lateral connections within itself. It could therefore select particular regions of the visual field and intensify or otherwise modify the signals being sent within such a region. There is increasing evidence that supports this conjecture (McAlonan *et al.* 2006).

The remainder of the first phase saw the publication of a brief note, suggesting a mechanism for the stability of long-term memory in the face of molecular turn-over within synapses (28).

Consciousness

Turning now to the second phase of Francis's work on the brain, consciousness is often assumed to be an emergent property of ensembles of neurons, arising in some way from the brain's entire neural activity. Francis and his collaborator during this phase, Christof Koch, took an opposed, extreme reductionist position, and postulated that consciousness is a consequence of the activity of particular neurons in the brain whose activity is correlated with some aspect of a conscious percept. They called the neuronal activity that manifests this kind of correlation the 'neural correlate of consciousness' or NCC.

This idea is in some ways very natural. Some of the activity in the brain seems not to be correlated with consciousness; for instance, the activity in the brainstem that controls breathing does not register consciously most of the time. Thus, one can argue, it is only

certain types of activity in particular brain regions that contribute to consciousness; if we can pin down these activity patterns, perhaps this will tell us something about the underlying mechanism of consciousness.

Francis and Koch set out on this path by arguing that activity in the primary visual cortex (V1) never contributes to the NCC (29). To put this in context, the cerebral cortex, the part of the brain thought to be associated with higher mental function, is divided into many regions or 'areas' that are specialized for various aspects of sensory or motor processing (Zeki 1993). There is a rough hierarchy for these areas, and V1 is the first in a succession of areas that carry out ever more elaborate types of visual processing. At the very start of visual processing, in the retina, one might expect there to be little or no correlation between neuronal activity and conscious percepts since the visual field of these neurons is very small and their activities fluctuate with eye motion in a way that is not consciously registered. Thus, the NCC must lie further up the pathway, and their claim is that V1 is still too early in the pathway for its neurons to exhibit the desired properties.

To support this claim, they consider a variety of experiments using special visual stimuli. For example, it is possible to create rivalry between the two eyes so that the orientation of a grid of lines appears to change from time to time even though the stimulus is constant. It can be shown in monkeys, trained to signal the percept with a lever, that the responses of orientation-selective neurons in V1 do not change with the percept, whereas neurons higher in the visual pathway, in an area called MT, are correlated in this fashion (Logothetis & Schall 1989). Thus, in this case the higher area MT seems to participate in the NCC whereas V1 does not.

The book by Koch, *The quest for consciousness* (Koch 2004), that sums up their joint work makes for enjoyable reading and is, at the very least, a thorough-going attempt to relate our knowledge of brain neurophysiology to subjective experience. A recent review of experimental work exploring the nature of the NCC (Koch *et al.* 2016) shows that the field is active. Yet their approach to consciousness can be questioned on many grounds. For example, how does one tell if neurons participating in the NCC are there in a supporting role or 'directly contribute' to consciousness? Can one trust people's reports of consciousness (for instance, when they are roused from sleep and asked if they were dreaming)? The lack of an operational definition of consciousness is a problem here, and indeed it could be considered an impediment to any truly scientific attack on consciousness, as Hopfield points out in his review of Francis's *The astonishing hypothesis* (Hopfield 1994). It also seems unlikely that the search for the NCC will illuminate what the philosopher David Chalmers calls the 'hard problem' of consciousness—how physical processes can give rise to subjective experience. At least this is the view of Chalmers, though Francis and Koch offer a rebuttal (30).

It is very much in character for Francis that he chose to focus on a clear reductionist hypothesis for consciousness, and if it proves provocative and controversial, that is not something that he would have shrunk from. Equally in character is the opening quote from *The astonishing hypothesis*, which gives Stuart Sutherland's verdict on consciousness: 'Nothing worth reading has been written on it' (Sutherland 1995).

On the day he died, Francis was working on a paper proposing that the claustrum, a deeply buried brain region with widespread connectivity to cortical areas, is important in integrating conscious experience (31). The last sentences are a rallying cry to neuroscientists to get on with the job of exploring consciousness: 'What could be more important? So why wait?'

Overview of Francis's brain research

Francis's great strength was, in Goethe's phrase, his 'imagination for reality'. He wanted to know as much as possible about the biological system he was studying and to identify the key questions, and if possible answer them. In this sense, he was inspired by the realities of biological science. It might seem odd to stress this, since after all science is about reality. Yet, there is a kind of theorizing about the brain that looks for mathematical abstractions and seeks to give the subject something of the feel of theoretical physics. Francis had no time for this approach. He wanted to understand what was going on. If the psychological evidence pointed to a 'searchlight', where was it? And if the brain is the seat of consciousness, well, where precisely is it located? These instincts worked magnificently in molecular biology. Only time will tell how well he succeeded in the brain.

Personal life

The first Crick family home in Cambridge was the 'Green Door', a tiny rented apartment in the Old Vicarage next to St Clement's church near the town centre. Even for 1949 it was primitive—taking a bath, in the kitchen, first required clearing cooking ware from the wooden bath cover. Their lifestyle greatly improved when they moved into a more permanent home in nearby Portugal Place, where Gabrielle and Jacqueline, sisters for Michael, were born (figure 15). Part of a tenement building and spread over five floors, its décor reflected Odile's artistry and became 'The Golden Helix', with an ostentatious golden helix over its front door. It was the venue for many vibrant parties of artists and scientists (figure 16). In the early 1960s, Francis and Odile bought a thatched cottage outside Cambridge, a country retreat with swimming pool and garden where Francis, surprisingly, became interested in growing roses.

Francis, always well-groomed, with bushy eyebrows, modest sideburns and usually sporting a colourful tie, was a debonair personality. His voice was rather high with a characteristic edge—difficult to miss at a gathering. His most striking feature was his *joie de vivre*. With an enthusiasm and mental penetration for understanding everything around him, coupled with a rare ability to communicate, he was exceptionally entertaining and thought-provoking; his personal entry in *Who's who* was 'Conversation, especially with pretty women'. Later, when they moved to California, he brought his flair and vitality with him. A large floppy hat was added to his attire, as protection against the sun. He and Odile found a beautiful house in La Jolla and designed and built a retreat at Borrego Springs where Francis cultivated cacti and other desert plants, perhaps the nearest thing to the roses in his English garden.

As an atheist, Francis gave several popular talks in Cambridge, such as 'Is vitalism dead?'. On this occasion, he opened by saying you can always identify a vitalist: in subsequent discussion he will imply some vitalistic force or law—and then hasten to add that he is not a vitalist. At the end of this talk, the very first question led to uproarious mirth: the innocent questioner ended by claiming 'But of course, I'm not a vitalist'! Francis loved poking fun at religion—he predicted that universities would soon have departments of molecular theology, in which the neuronal modifications effected by praying would be understood. When Hugh Montefiore, the Vicar of Great St Mary's in Cambridge, whom Francis knew well from their Caius connections, opined at a meeting in Oxford that Jesus might have been gay—an item which led the *BBC News* of the day—Francis jested that it could not be long before they made him a bishop. This duly happened three years later! Francis was deeply interested in the origins

Figure 15. Family group, 1956. From left: Jacqueline, Odile, Michael, Gabrielle and Francis. (Courtesy of the Crick family.)

of life. His friend, Leslie Orgel, had found conditions in which the chemical units of nucleic acids might be formed. Together they worried about how, in a primeval soup, the sequence of an individual nucleic acid might assist in the formation of a particular polypeptide sequence, and that polypeptide then favour that particular nucleic acid? Once achieved, natural selection could begin to operate. They also wondered whether life started here on Earth, or elsewhere: this led to an article on directed panspermia (20).

Occasionally, Francis deployed his political skills. The NATO-sponsored annual Spetsai summer schools were instigated by his friend, Marianne Grunberg-Manago of Paris, in 1966 to help retain some molecular biology in Europe as it became increasingly dominated by the US. Francis attended several of these; lasting a fortnight, they provided an opportunity to relax on a small Greek island, chat with a variety of friends and then sail around the Greek islands in his boat, the *Eye of Heaven*. The 1967 meeting, due to be organized by Brian Clark and MSB of the LMB, had to be cancelled at the last moment because of a government coup by 'The Colonels'. The 1968 meeting was also cancelled, but Francis, as our guide, decided that in 1969 it should proceed. There was much opposition to this from the Continent, but Francis was insistent. He wrote to the Greek Government asking for assurances, should the meeting go ahead, that:

1. As in previous years, any student accepted from behind the Iron Curtain (usually about 20 students) be given a visa for the length of the meeting.
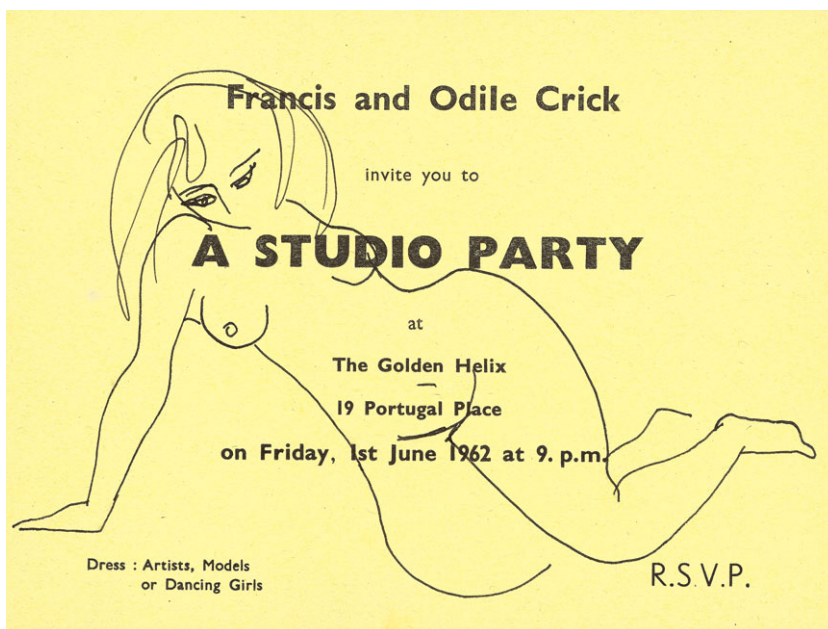
Figure 16. 'A Studio Party' invitation, June 1962. Image designed by Odile. On arrival at the party, guests were provided with a pencil and artist's pad to sketch a reclining nude model. After an hour or so the party became more conventional, with drinks and dancing. (Courtesy of the MRC Laboratory of Molecular Biology.) (Online version in colour.)

2. The existence of the meeting would not be used for any propaganda purpose.
3. No minister or other official of the Greek Government could attend the meeting.

These assurances, which required Greece temporarily to cede sovereignty in determining who would be granted a visa to the organizers, were given and the school went ahead. During the meeting, a group of largely German students decided to form a protest against the Greek Government. Francis called a meeting of all participants and explained to them the assurances he had been given by the Government, and that if any such demonstration occurred, he would immediately cancel the rest of the meeting. The protest died.

Francis was a Founding Fellow of Churchill College, but resigned from that post when the College, with John Cockcroft FRS as Master and a devout Christian, agreed to build a chapel. Francis thought religion had no place in a modern institution of learning, such as a Cambridge college. He explained his decision to Winston Churchill, who replied that 'a chapel is an amenity which many of those who live in the College may enjoy, and none need enter it unless they wish'. Francis must have greatly relished shaping his reply to a former First Lord of the Admiralty—it reflects his innate entertaining skills and forceful powers of expression:

Dear Sir Winston,
   It was kind of you to write. I am sorry you do not understand why I resigned.

To make my position a little clearer I enclose a cheque for ten guineas to open the Churchill College Hetairae fund. My hope is that eventually it will be possible to build a permanent accommodation within the College, to house a carefully chosen selection of young ladies in the charge of a suitable Madam who, once the institution has become traditional, will be provided, without offence, with dining rights at high table.

Such a building will, I feel confident, be an amenity which many who live in the college will enjoy very much, and yet the instruction need not be compulsory and none need enter it unless they wish. Moreover, it would be open (conscience permitting) not merely to members of the Church of England, but also to Catholics, Non-Conformists, Jews, Moslems, Hindus, Zen Buddhists and even to atheists and agnostics such as myself.

And yet I cannot help feeling that when you pass on my offer to the other Trustees — as I hope you will — they may not share my enthusiasm for such a truly educational project. They may feel, being men of the world, that to house such an establishment, however great the need and however correctly conducted, within the actual College would not command universal support. They may even feel that my offer of ten guineas to be a joke in rather poor taste.

But that is exactly my view of the proposal of the Trustees to build a chapel, after the middle of the 20th century, in a new college and in particular in one with a special emphasis on science. Naturally some members of the College will be Christian, at least for the next decade or so, but I do not see why the College should tacitly endorse their beliefs by providing them with special facilities. The churches in the town, it has been said, are half empty. Let them go there. It will be no further than they have to go to their lectures.

Even a joke in poor taste can be enjoyed, but I regret that my enjoyment of it entailed my resignation from the College which bears your illustrious name.

Understandably I shall not be present on Saturday. I hope it all goes off well.

Yours sincerely,

Francis had a keen sense of humour. In 1962, at coffee one morning with Jim and a few others, Jim suddenly opined that he had just realized what he would really like: an oil painting of Francis sitting on a horse! Quick as a flash Francis quipped, 'But Jim, it wouldn't be complete without you there, holding the bridle.' Later, in the mid 1970s, he enjoyed recounting a stop at a motel whilst travelling around California with Odile. At the registration, the bellhop asked Francis his name. 'Crick', he says. The bellhop queried, 'You mean, like in Francis Crick?'

What made Francis such an outstanding theoretician? Curiosity about the world around him. He was undoubtedly clever, having a very fast mind and an artistry for visualizing structures in three dimensions. He possessed an optimistic belief that problems could be solved. A bit like an 'intellectual nuclear reactor', according to Oliver Sachs. Unfettered by preconceptions, he used his amazing imagination and tenacity to strip away those parts which he thought were peripheral, searching for a simplified way of thinking about how it might be, or for any underlying pattern or principle. In constructing a new hypothesis, it should cast a broader beam than the original spotlight, bringing seemingly unconnected facts into focus. He had a couple of devices to help him in this. If the whole seemed to hang together save for some awkward aspect, he placed this feature in a 'don't worry' box. Thus, when he and Jim realized that copying each DNA strand by base-pairing could explain how genetic information is duplicated, the obvious problem arose: how are the new intertangled strands separated? 'Don't worry' took care of it. Another helpful ploy was the 'black box': if there was a self-contained obstacle in a larger intellectual scheme, the impediment could be treated as a black box and put to one side. An example he often cited is the ribosome. In

the 1960s, its overall function was clear, yet the mechanics of how it translated a nucleic acid language into a peptide language was a mystery, one which is now well understood. In his autobiography (1988), Francis attributed much of his skill to observing how Bragg tackled problems, 'realizing that many apparent complications might fall away if the basic underlying pattern could be discovered'.

In the different phases of his scientific career, Francis found long-term colleagues and friends who shared his broad outlook on the problem at hand and who complemented him with their knowledge. He sought advice and help from his life-long friend Georg Kreisel (FRS 1966), mathematical logician and free-thinker whom he met in World War II. It was Kreisel who repeatedly asked Francis why a problem he was fretting over was worth understanding, a question Francis would frequently pose to others. He formed close partnerships with Jim and later with Christof Koch. However, his long collaboration with Sydney Brenner was especially fertile. Both were deeply interested in genes, and how the biological information held in them is used to shape an animal. When they were pondering over a problem, each could see almost effortlessly why the other thought, or suggested, what he did. Their intellectual fit was astonishingly creative.

For someone with such a quick mind and impatient with careless or sloppy thinking, Francis was a surprisingly good listener. Perhaps there was another view, or something interesting to learn? He frequently confessed to having a terrible memory, but that was not true. The hard experimental facts he remembered: they anchored his thinking. Matters he regarded as peripheral were often forgotten. Few theoreticians pay so much attention to experimental detail as he did. In reading an experimental paper, he did much as an experimental scientist might: look at the quality of the pictures or data and then turn to the experimental section to see how the results were obtained and ask oneself why one approach, rather than some other, had been taken. His early experience in trying to purify proteins led him to appreciate how demanding experimental biochemistry can be. He also knew that many experimental observations are loosely interpreted and therefore one must grasp the unshakeable experimental facts, not the interpretations offered.

Francis learned in 2001 that he had advanced colon cancer. He continued to think and write about the brain until he died in 2004; Odile died in 2007.

In a tribute to Francis, Aaron Klug ended by saying: 'it is hard to believe that that penetrating intellect and powerful personality has been extinguished. But he will be remembered as one of a select few who created a new science, and his name is likely to live in biology with that of Darwin.'

Awards and honours

1959   Elected Fellow of the Royal Society
1960   Lasker Foundation Award
1961   Grand Prix Charles Leopold-Mayer
1962   Gairdner Foundation Award
         Nobel Prize in Physiology or Medicine (shared with Jim Watson and Maurice Wilkins)
1966   Croonian Lecture of the Royal Society
1972   Royal Medal of the Royal Society

1975 Copley Medal of the Royal Society
1991 Order of Merit
2001 Benjamin Franklin Medal (shared with Jim Watson)

Francis Crick's contributions have been recognized in different ways: there is a stained-glass window and pavement memorial in Gonville and Caius College, a sculpture in Northampton and a vast MRC Institute ('The Crick') in London. In addition, postage stamps celebrating Francis Crick have been issued by Zambia, Palau and Sweden.

Books

Francis wrote four books, which depict his scientific philosophy and thoughts about religion and society:

> *Of molecules and men* (1966)
> *Life itself: its origin and nature* (1981)
> *What mad pursuit: a personal view of scientific discovery* (1988)
> *The astonishing hypothesis* (1994)

Two biographies of Francis have been written: *Francis Crick: discoverer of the genetic code* by Matt Ridley, a highly readable account of Francis's life, and *Francis Crick: hunter of life's secrets* by Robert Olby. Olby's excellent book carries many interesting details and anecdotes of Francis's life and has been a valuable source of information for this Memoir.

Acknowledgements

Author profiles

Mark S. Bretscher

As a research student, I joined the MRC Unit in the Cavendish Laboratory in September 1961. Francis arranged for me to test the coding properties of synthetic polynucleotides in an *in vitro* system, using various RNAs prepared by Marianne Grunberg-Manago of Paris. This led me to find and elucidate the structure of a new intermediate in protein synthesis—the peptidyl-tRNA complex and the discovery of termination codons. After a postdoc with Paul Berg, I joined the staff of the Molecular Genetics division and worked on different aspects of protein synthesis—chain initiation, termination and translocation. In 1969, I studied the structure of the erythrocyte membrane—discovering that proteins span the membrane and phospholipid

asymmetry. Thereafter, I worked on endocytosis and the mechanism of cell locomotion. Until Francis moved to California, he followed my progress carefully and offered advice, mainly about diffusion in membranes. I was head of the Cell Biology division (Crick's old post) from 1985 to 1994.

Graeme Mitchison

I joined the MRC Laboratory in 1969, having just finished a DPhil in mathematics at Oxford (and having realized that pure mathematics was far beyond me). I was assigned to Michael Wilcox, who, with infinite patience, tried to teach me how to be a biologist. Michael, Richard Smith and I worked out some of the rules that underlie the development of the heterocyst pattern in blue–green algae. Following that, I studied the development of higher plants for a few years, taking up the ideas of the remarkable Israeli botanist, Tsvi Sachs. Francis then suggested that I should join him for two years at the Salk Institute. The upshot of this is described in the section 'Thinking about the brain'. I returned frequently to the Salk after that to see Francis, though my primary interest had by then become the study of visual perception, which I pursued in Horace Barlow's group at the Physiological Laboratory in Cambridge.

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