



Francis H. C. Crick, 2004 (photograph by I. and M. Hargittai).

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# FRANCIS H. C. CRICK

Francis Harry Compton Crick (1916, Northampton, England – 2004, La Jolla, California) at the time of his death was a distinguished research professor of the Salk Institute for Biological Studies in La Jolla, California. He was also a former president of the Institute. He was co-recipient of the Nobel Prize in Physiology or Medicine for 1962 together with James D. Watson<sup>1</sup> (b. 1928) and Maurice Wilkins (1916–2005) “for their discoveries concerning the molecular structure of nuclear [*sic*] acids and its significance for information transfer in living material,” in short, for the discovery of the double helix structure of DNA.

Francis Crick attended Northampton Grammar School, then Mill Hill School in North London. He studied physics at University College London and received his B.Sc. degree in 1937. He continued his studies for a doctorate, doing research on high-stress failure in engineering materials. His studies were interrupted by the war, and he did war-related research for the British Admiralty during World War II. In 1947, he started doing research for the Medical Research Council and from 1949 he worked at the Cavendish Laboratory of Cambridge University. His cooperation with James Watson started in 1951, and led to the discovery of the double helix in 1953. During the subsequent years he continued working in molecular biology, primarily involved in the understanding of protein synthesis and the genetic code. He left Great Britain and joined the Salk Institute in 1976 and changed his research fields for understanding the brain and the nature of consciousness.

Francis Crick was a Fellow of the Royal Society (London); a Foreign Member of the National Academy of Sciences of the U.S.A. (1969),

and other learned societies. His many honors included the Lasker Award (1960), the Gairdner Award (1962), and the Prix Charles Leopold Meyer of the French Academy of Sciences. In 1991, he was named a Member of the Order of Merit of the United Kingdom, whose membership is restricted to 24.

This account is about a conversation with Francis Crick and his wife Odile Crick a few months before his death and about my (IH) correspondence with him over the years.

## The Visit

My wife, Magdi and I visited Francis and Odile Crick in their home in La Jolla, California, on February 8, 2004. It was a full two hours of conversation over lunch. I had written to Crick about our forthcoming visit to Pasadena, and he had written to me: "My health is still poor but it would be a pity for us to be so close and yet not meet. So I suggest you come to lunch on Saturday, February 7th at my house in La Jolla, arriving between 12:30 and 1:00 p.m. Attached is a crude map to help you find our house." This was our first and only personal meeting. When we rang the Cricks' bell, Francis Crick opened the door, Magdi stepped in first, and Francis stretched out his hand and introduced himself, "I'm Francis Crick." There was also Odile right away, and the two of them made the atmosphere so light and pleasant that I could not help telling them at once about what I had just read in Maurice Wilkins's new book, *The Third Man of the Double Helix*. Wilkins writes about his trying hard to find someone to marry and hoped that Crick and Odile would bring some nice young woman with them. Wilkins adds that he had no wish to separate Odile from Francis. Francis and Odile laughed heartily at Wilkins's "magnanimity".

Our conversation covered many topics. Erwin Chargaff's name came up and Francis found it strange that Chargaff did not discover base-pairing in the light of his observations on the base ratios in DNA. However, this may be more surprising in hindsight. Just looking at the data, there is much fluctuation, about 10 per cent, about the 1 to 1 ratios. So even recognizing and suggesting the 1 to 1 ratio was a sharp observation. Francis then added that Chargaff's mind might have not wandered towards pairing because he, that is, Chargaff was thinking in terms of one chain rather than two. In a single chain, nothing would prompt one's thinking towards pairing. Once you know that two chains need be considered, pairing enters

one's thinking more naturally. Francis seemed careful not to use the word helix at this point, as if placing himself into Chargaff's position. Even if Chargaff was thinking about the significance of the 1 to 1 ratios, about the possible meaning of such a ratio in a nucleotide chain, it's not surprising that nothing suggested itself for a reasonable solution.

Once the idea of two chains or helices came up, base-pairing was more probable to be thought of. That it was not trivial is witnessed by the fact that Crick and Watson did not think of base-pairing either until the very last moment in the story of the discovery. It was very late in the story that complementarity came up. Even when Watson was pairing bases, first he was seeking correspondence between like bases. Francis gently reminded me that solving the problem was less straightforward than I might have thought. Complementarity could have been accomplished between like bases if the two like bases would not be turning toward each other with the same end. When they started thinking about pairing bases though, whether like to like or between different ones, the solution was found relatively quickly. As Crick was talking about finding base-pairing, he distinctly spoke about "our" and not just Watson's findings. Watson did not even want to believe in base pairs initially.

Another feature of the double helix structure that we talked about in detail was  $C_2$  symmetry. Here, Francis said that Jim did not understand its significance. This is in accord with my own experience when we were in Cold Spring Harbor in 2002 and I talked with Jim about it. My impression was that even almost 50 years after the discovery, he still underestimated the significance of  $C_2$  symmetry in the DNA structure and in particular, in the story of the original discovery. This symmetry is the most unambiguous indication of the complementarity of the two helices. Francis added that Rosalind Franklin did not quite recognize the significance of  $C_2$  symmetry either in solving the DNA structure. Although Franklin was a crystallographer — and more so than Watson — she had never solved a structure before. She did not have extensive experience in structure analysis and even less with organic systems and polymeric molecules at that. Of course, nobody else had much experience with solving organic polymeric structures either, at that time. Crick thought that Wilkins speaks about base-pairing in his book as if he knew more about it than he could have and did at that time. Crick was sure that Wilkins did not have the idea at the time.

He told us that one of his most important findings had never been written up and was recorded only in a manuscript for a lecture which

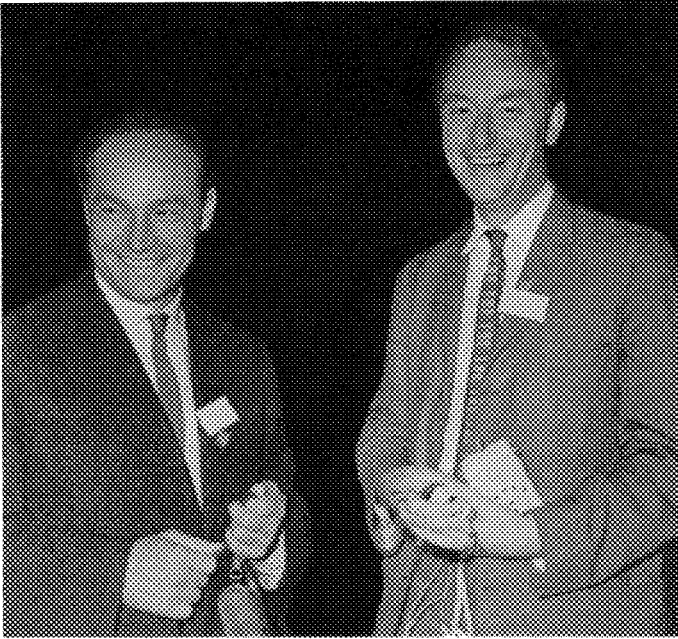
seems to have been lost. This was about the one-dimensional sequence of the amino acids in proteins and the importance of the three-dimensional structures of the proteins. The sequence, which was one-dimensional, determined the folding, which produced the three-dimensional structure. In terms of replication, the three-dimensional structure could not replicate itself; the only part that was capable of replication was the surface of the three-dimensional structure. The essence of the idea was that for replication it sufficed to repeat the sequence. Crick told us about this idea when I raised the question about who was the one that for the first time brought up the idea that the nucleic acids code for the proteins. Then he said that actually he had this idea, but, he added, then others also had this idea.

When we talked about the connection between nucleic acids and proteins, Francis said that Jim and he were definitely thinking about that in the spring of 1953. When they announced on that fateful day in the pub, The Eagle, that they solved the secret of life, they could make such an announcement only because they realized that there was a connection. For calling it the secret of life, the double helix structure of DNA would not have sufficed. They understood the implication of the double helix so quickly because they had thought about the question of information transfer.

Actually, Crick told us, he had had this idea even before he had met Jim Watson. This is fascinating as we may try to delineate their contributions to the story of the double helix. When they worked together, they talked a lot to each other, so it is hardly possible to delineate their contributions. In raising this question about how nucleic acids code for proteins, it is very difficult to delineate their shares. However, this idea about the importance of sequence in replication, whether it is the sequence in nucleic acids or proteins, was Crick's idea alone.

We also talked about Jim and Francis enumerating the 20 naturally occurring amino acids. This was in connection with the notion that sometimes it happens that important findings do not appear so important at the time of their being made. Today, this enumeration is there in every textbook, but seldom is it associated with Crick and Watson.

A good part of our conversation concerned religion. I started with the general notion by Jim Watson that he was not happy that Crick seemed to have been moving from a more radical position towards the center. According to Jim, Francis was in a better situation to criticize religion



Jacob (Yakov) Varshavsky and Francis Crick in Moscow at the Fifth International Congress of Biochemistry, 1961 (courtesy of Alex Varshavsky).

than he was himself. This was because Francis was not the head of a major organization and he was not involved in fundraising as he, Jim, was. Crick said that to fight religion at the present time produces only frustration. First we have to understand how the brain operates and after that it will be much easier to convince people that religion is meaningless. We also talked about the recent changes in the views of the Catholic Church regarding evolution, for example. Francis stressed, however, that the Catholic Church seems to want to solve all the problems of religion within its own framework and without the involvement of science.

Francis had high hopes for the success of the new book about the mind, *The Quest for Consciousness*, by Christof Koch.<sup>2</sup> He told us that the book was the result of their joint work, but Koch was the sole author; Francis authored only the introduction. We talked about the importance of book titles and we learned that Odile had something to do with the final title of this book. She suggested replacing the initially used “search” by “quest”.

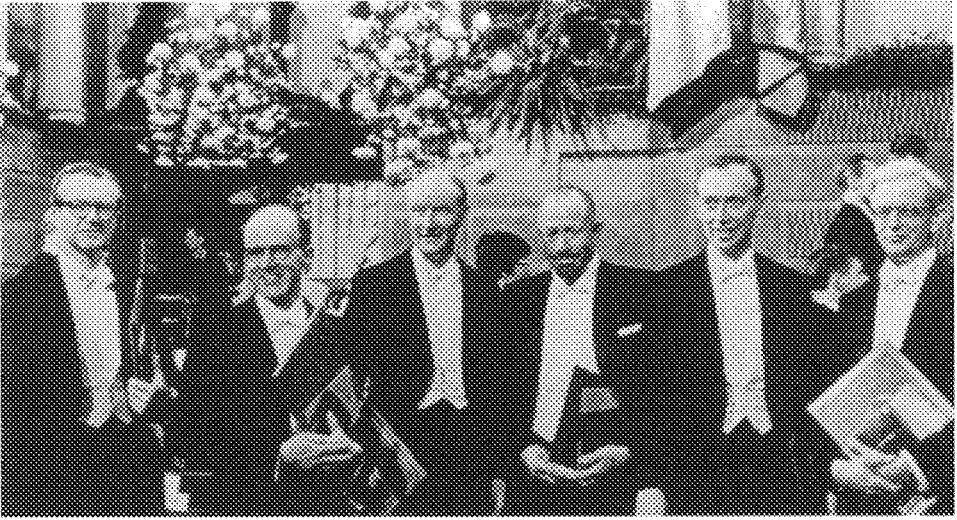
I told Francis that we very often ask the question in our interviews about heroes. Of our contemporaries Francis Crick is mentioned more often than anybody else is (of the non-living, Albert Einstein is mentioned most often). Francis was not shy about this and appeared pleased and genuinely interested in what the reason might be. We mentioned one example, that of Fred Sanger. Sanger liked Crick's style of lecturing, the ease with which he did it, and the jokes he inserted into his lectures. At one point Sanger decided to emulate Crick. He had carefully prepared his presentation in Crick's style, but he came away disappointed because all his jokes came out flat and were received with silence. Francis enjoyed the story and I understood what it meant when people described him as roaring with laughter. He said that it did not work this way. He never prepared his jokes specifically although they came out of his reservoir; but they came out — or appeared coming out — spontaneously during the talk. Once he was asked to give a lecture in Paris but he was asked to give it in French. His French was not that good, so he wrote it up and Odile corrected and translated it. The first thing that had to be left out was the jokes; it would have been difficult to have his old jokes in French, besides, planning them in advance — so that they could be translated — made it impossible for them to appear as spontaneous jokes.

When I asked Francis about his heroes, he mentioned Linus Pauling. He also added that he was a latecomer in science, and people “worship” heroes when they are younger. Francis was about 30 years old when he started in science.

I knew that Francis was gravely ill, yet there was no impression of illness during our meeting. It was an unforgettable encounter for us and it gives me a good feeling that Francis and Odile visibly enjoyed our visit. Maybe it meant a brief break away from gloomier times that in less than half a year would end in Francis's death. I cherish all that I learned from him in our conversation, but we have what he told us through the filter of our memory. What he wrote me in our correspondence is of course a more reliable record.

## The Correspondence

Over the past few years, I sent a few letters to Francis Crick with questions that I thought only he could answer. I wrote him on July 24, 2000, asking him about the story of the introduction of the isomorphous replacement



Maurice Wilkins, Max Perutz, Francis Crick, John Steinbeck, James D. Watson, and John Kendrew in Stockholm, at the Nobel Prize ceremony, 1962 (courtesy of the late Lars Ernster).

method into protein crystallography. In our book with Magdi, *In Our Own Image*,<sup>3</sup> we quoted Max Perutz who — with reference to the hemoglobin structure — told me a few years before the following: “In 1953, I discovered that it could be solved by the method of isomorphous replacement by comparing the X-ray diffraction pattern from a crystal of pure hemoglobin to one from hemoglobin to which I attached two mercury atoms.” At the time of writing our book, we were a little puzzled that he did not mention J. M. Robertson, David Harker, and J. M. Bijvoet, who originated the technique of isomorphous replacement although they never applied it to proteins.

In Crick’s book, *What Mad Pursuit*,<sup>4</sup> I noticed that he might have been the first at the Cavendish Laboratory to suggest the use of the isomorphous replacement method in protein structure analysis. Crick was unambiguous in his response saying that he and others might have made such suggestions, but it was Perutz who carried out the tremendous amount of work that was involved and the credit should be his alone.

I wrote Crick again in early spring of 2001. I had just completed the manuscript of *The Road to Stockholm*.<sup>5</sup> I wondered about the missing Nobel Prize for Sydney Brenner. I knew that Brenner and Crick used to work together in Cambridge and that they had a sizzling intellectual interaction

for years. However, I felt that from the point of view of the Nobel Prize, theirs was an asymmetric relationship. Whereas Crick had already had his Nobel Prize, the assignment of any major research achievement to Brenner might have been hindered by his close relationship with Crick. So I asked Crick about this. Here is what he wrote me on April 13, 2001:

Although Sydney Brenner and I shared an office for 20 years, for most of that time I worked in the office (not always the same office) whereas Sydney worked mainly in the lab. However we did talk together for an hour or more on most days.

The adaptor hypothesis was my idea, but Sydney coined the name for it. Sydney had the idea that acridine mutants were probably the addition or subtraction of bases. I did all the initial work on the phase-shift mutants, but Sydney designed the special genetic cross to show that +++ mutants were like wild-type. I worked out that shifts to the left were different from shifts to the right. Sydney did almost all the work to establish the stop-chain codons. Sydney realized that the Volkin–Astrachan DNA was really messenger RNA, though I immediately saw it too. Sydney, with Meselson and Jacob, established the existence of mRNA experimentally. Sydney (and another group) established experimentally the co-linearity of gene and protein. My recollection is that all this is fairly accurately described in Horace Judson's book, *The Eighth Day of Creation*.

All the initial work on the nematode was conceived and carried out by Sydney, and he organized the study of its cell lineage and its detailed neuroanatomy.

In my opinion Sydney ought to have the Nobel Prize but although he has done a vast amount of important work it is difficult to select just one particular discovery that would attract a Nobel Prize.

However Sydney's work is widely recognized by everyone. In fact he has received every other important award other than the Nobel — many more than I have!

I hope this is of some help. Incidentally, *What Mad Pursuit* is mostly about the mistakes I made.

This letter was only 18 months before Brenner's long-awaited Nobel Prize was announced.

In my letter dated April 26, 2001, I asked Crick about what Jim Watson told me in my interview with him<sup>1</sup>: “Francis Crick gave a provocative lecture in 1968 at University College London where he said you should only be declared alive two days after birth. Later I have been mistakenly accused of that remark — Watson continued — ascribing to me Hitler-like motivations. Francis also then said the state should not spend any money for medical care about people above 80. Now that he is 84, he would probably disagree. He said this when he was 52.” Crick responded on June 28, 2001, and I quote from his letter:

My apologies for not replying sooner to your letter of April 26th. I did indeed give a provocative lecture in 1968 (or thereabouts) at University College London, but I’m not sure that I still have a copy of it.

To reply to your two questions I would indeed modify my suggestions today. In the old days doctors quickly let a very deformed or handicapped baby die, rather than make exceptional efforts, as they often do now, to keep the baby alive. I now realize that it would be impossible, at least in this country, to count life as starting after the first two days of a baby’s life because so many religious people believe life effectively starts much earlier, even at conception. In other words one has to consider not just the feelings of the baby (who hardly has any) but also the feelings of the parents, and of other members of society, however silly one may think them to be. But I do believe that doctors should not make exceptional efforts to keep a very handicapped baby alive.

As to the age limit, people now live longer than they did in the sixties, so I think such an age might be a little higher, but I doubt if a rigid rule would be acceptable. Again I think very expensive treatments, or ones that have only a limited availability, should be allocated in some sensible way. I’ve heard that the State of Oregon is trying out such a scheme.

If I were to give such a lecture again (which is unlikely) I would instead stress the right of a person who is incurably ill to terminate his own life. I believe this is being tried out in Holland.

In my next letter of July 27, 2001, I asked him whether there were any scientists that could be considered directly as his pupils. I found this

question of interest because by then I had experienced that other famous scientists named Crick more than anybody else among living scientists as their hero. Again, Crick's response of August 1, 2001, is of interest in full:

To reply to your question, I don't think there is anyone whom I could call my pupil. I only supervised a graduate student for a year, but after that year someone else took him over. I think I deliberately avoided such tasks.

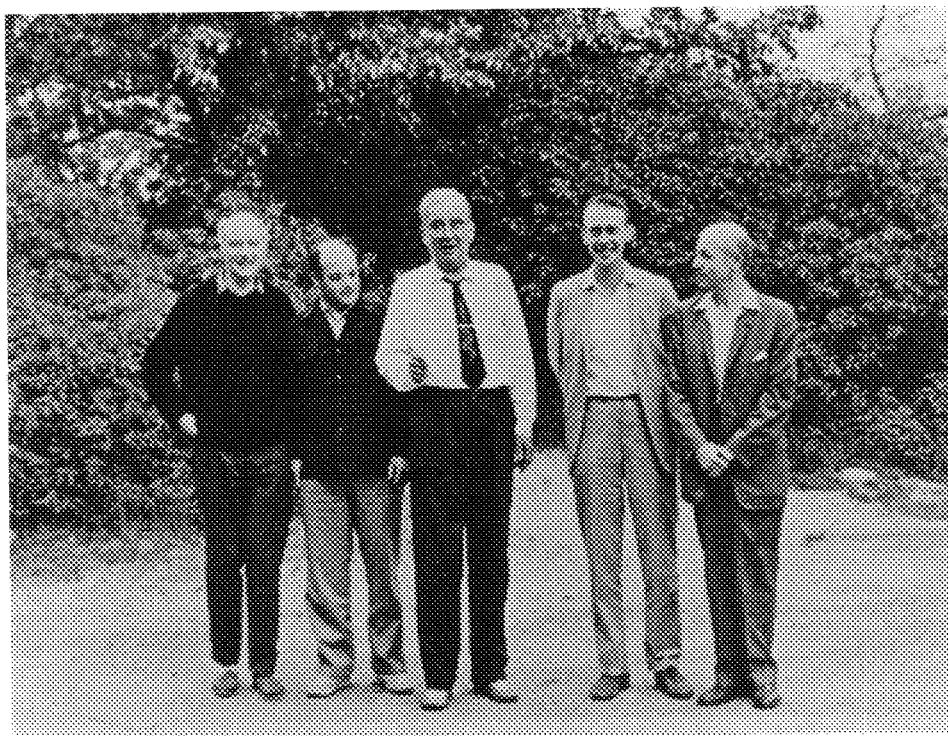
On the other hand I have had several close collaborators. The major ones have been Jim Watson, Sydney Brenner and (more recently) Christof Koch. Others I have had more than transient collaborations with are Aaron Klug, Beatrice Magdoff, Leslie Orgel and Graeme Mitchison. In all these collaborations we have published papers together. These collaborators (except possibly for Magdoff and Mitchison) have each had many pupils of their own.

I think I work best, not entirely by myself, but with one other close collaborator. Sydney Brenner and I shared an office for 20 years. At the moment my close collaborator is Christof Koch, a neuroscientist at Caltech.

Of course I have interacted for most of my scientific life with a very large number of scientists and over the years have given lectures in many different places. Some people have told me that they were strongly influenced by a lecture of mine they heard. I think I must have been rather a good lecturer, because at meetings no one liked to have to lecture after me!

Finally, in my letter of August 8, 2003, I asked Crick several questions. During the summer of 2003, I was preparing a talk "Success in Science" for the Ph.D. students of the Karolinska Institute at their annual retreat in the Stockholm Archipelago in September. During the preparation, I had several questions that I decided to pose to Crick. I need to describe my questions in some detail because Crick would refer to them in making his responses succinct.

1. George Gamow. I have had the impression that the molecular biologists did not quite appreciate his ideas for the genetic code. On the other hand, the backs of the photographs I had received from the University of Colorado



Francis Crick, Alex Rich, George Gamow, James D. Watson, and Melvin Calvin at the Cold Spring Harbor Laboratory (courtesy of J. D. Watson).

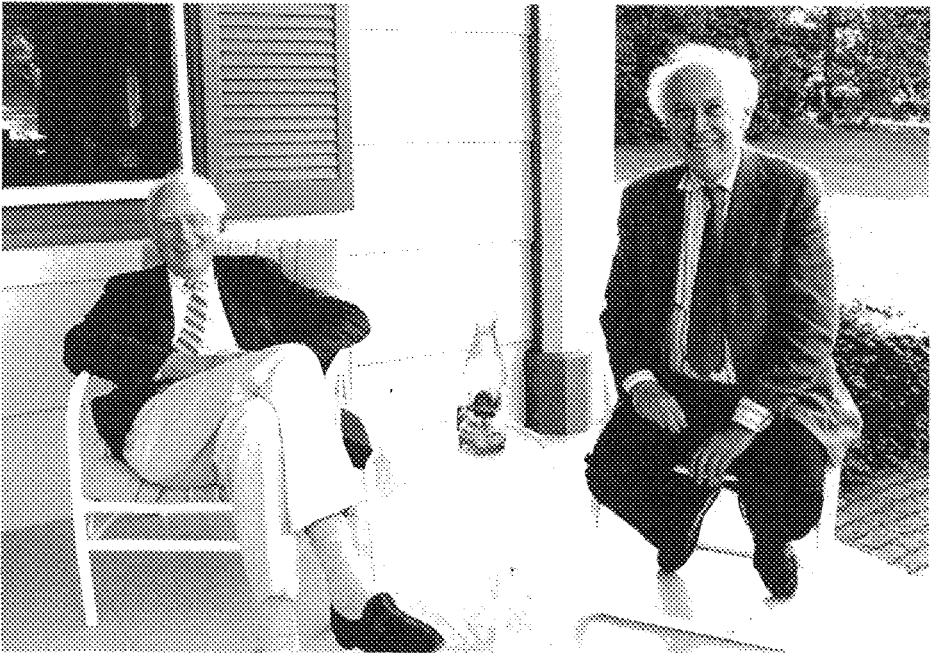
on Igor Gamow's behalf indicated Gamow as "the originator of the triplet code". In my conversation with Arno Penzias, when we considered Gamow's place in science history, he told me that Gamow was a better scientist than Galileo.<sup>6</sup>

2. Religion. Gunther Stent told me<sup>7</sup> that he wrote an essay for the 20th anniversary of the double helix in which he presented a linguistic analysis of some of Crick's writings. Stent substituted the word "God" wherever Crick had used the word "nature". According to Stent, the substitution did not change the essential meaning of the text. Privately Crick let him know that he didn't like what Stent implied. I also asked Crick for comment in connection with the Church's recent acceptance of the idea of evolution. I mentioned Wigner's position that physics did not endeavor to explain nature; it only endeavored to explain the regularities in the behavior of objects.

3. When Crick was searching for a research area, he seemed very lucky to have the possibility of consulting always top people, like the Nobel laureate A. V. Hill. I asked him how did this happen.

4. I once again returned to the question about the evaluation of Perutz's contribution to protein crystallography.

5. I asked Crick about J. D. Bernal who could have been included in the 1962 Nobel Prize in Chemistry that went to Perutz and John Kendrew or in the 1964 Nobel Prize in Chemistry that went to Dorothy Hodgkin although nobody protested that Bernal was not included. Bernal was also a pioneer in protein crystallography, if only considering his taking the first ever X-ray pictures of a protein with its mother liquor. My impression was that although Bernal might have had seminal contributions, he did not live up to his own enormous potentials. His communist politics might have also hurt him when recognition (and research support) was concerned.



Francis Crick and James D. Watson in Cold Spring Harbor Laboratory, 1990 (courtesy of J. D. Watson).

6. My next question concerned the importance of  $C_2$  symmetry in describing the double helix structure of DNA. In one of my conversations with Jim Watson, I had suggested an alternative description of the double helix using a more technical language of symmetry than the original description of the Watson–Crick announcement in *Nature*. Jim had dismissed it saying that the knowledge that the structure had  $C_2$  symmetry was not essential. I also asked Crick whether Rosalind Franklin was ever told during the last five years of her life after the double helix discovery that Watson and Crick had had access to her data.

7. Finally, I asked Crick whether he had any comment on the topic of “Success in Science”.

Here is Crick’s response dated August 29, 2003:

I am in poor health so I will respond only briefly to the long list of questions in your letter of August 8th.

About Gamow, I liked him very much, especially as he was very kind to two such junior scientists as Jim and me. He did not originate THE Triplet Code — his triplet code was completely wrong. I am not sure that he was the first to introduce the idea of triplets. (Sir Cyril) Hinshelwood had a silly argument for pairs, but it’s possible Dounce had earlier suggested triplets.

I would rank Galileo far above Gamow, because he was the first real scientist (with the possible exception of one or two Greeks, such as Archimedes). That is, he both did experiments as well as mathematics (or quantitative thinking) as opposed to thinking in words, as for example Aristotle did. Aristotle made many perceptive observations (not all completely correct, however) but he never did an experiment to test his ideas. When Newton said he was “standing on the shoulders of giants” one of the people he had in mind was Galileo. Galileo’s trouble with the Catholic Church has been exaggerated, and was mainly due to the Inquisition, a quite inexcusable institution.

I will not otherwise comment on Gamow’s place in modern physics. I certainly think he was original.

Gunther Stent, as usual, has produced an entertaining mixture of sense and nonsense. I will only say that my position is that

I am an agnostic, with strong inclination towards atheism. For Gunther's term "nature" I would prefer "The Entire Universe". I agree with Wigner that a little modesty would not be out of place.

I will not comment on the so-called "religious" views of Einstein and Bohr. Gunther's remarks about Babylon, etc. miss the point, which is that Darwin effectively discredited "The Argument from Design" which before him seemed unanswerable. Enough of my old friend Gunther! Incidentally he wrote an excellent review of the six reviews of Jim's book in the Norton edition of it.

By "The Church" I presume you meant the Catholic Church. All the "religions of the book" (the Bible) differ substantially among themselves. All three have both extensive sects and sub-sects. A recent encyclical by the present Pope said evolution must now be regarded as a fact, though it disapproves of what I do now. But in the U.S.A. millions of, say, Southern Baptists think evolution is quite wrong, that the earth is less than 10,000 years old, etc.

As to A. V. Hill, the MRC and so on, Bob Olby (who is writing my biography) has recently covered this in his draft. You could consult him about it.

About Max Perutz. He was certainly not the first to suggest the method of isomorphic replacement for proteins, but he was the first to make it work and this transformed the field. I don't think he was especially quick in applying it. This is because it is not easy to do. We had taken on Vernon Ingram to develop chemical methods to do this, so it was lucky Max got a supply of sickle cell hemoglobin AND the Hg worked. He did a wonderful job of sticking with hemoglobin till he had proved his theory of its action correct. Also in running the LMB so well and so smoothly. About his and Kendrew's Nobel Prize, I have always suspected that the major influence was Tiselius, but wait and see!

I agree with your comments on Bernal.

About  $C_2$  symmetry and DNA. I enclose a letter I wrote to Mark Bretschler about this. Whatever Jim may say, a few days before he discovered the base-pairs he was still building

models with parallel DNA chains and the bases paired like with like.

It was surely obvious (to us and to her) that Rosalind knew all the facts we might be expected to know, since she gave them in her 1951 seminar that Jim attended — though Jim forgot them all, including the  $C_2$  symmetry. The striking picture of the B form which she had put on one side for six months, and which I myself never saw till later, certainly excited Jim and made it easier for him to persuade Bragg to let us build models again.

Much later she told Aaron Klug that one thing she regretted in it all was missing the implications of the  $C_2$  symmetry. Incidentally Klug recently gave an accurate review of it all, and is writing it up for publication. You should always follow Klug about Rosalind. Brenda Maddox's interesting book is not scientifically accurate.

Success in science can take many distinct forms. I think I once said, "It was partly a matter of luck, and partly good judgment, inspiration and persistent application."



Odile and Francis Crick and István Hargittai in the Cricks' home in La Jolla, California, 2004 (photograph by M. Hargittai).



Odile and Francis Crick and Magdolna Hargittai in the Cricks' home in La Jolla, California, 2004 (photograph by I. Hargittai).

Best of luck for your lecture at the Karolinska Retreat. If you would like you could send me your impressions of it, but please don't expect me to reply again.

Then came our meeting on February 8, 2004, in La Jolla.

### References and Notes

1. In 2000–2002 we recorded several conversations with Jim Watson. Excerpts from the first one appeared in Hargittai I., *Candid Science II: Conversations with Famous Biomedical Scientists*, edited by M. Hargittai. Imperial College Press, London, 2002, pp. 2–15.
2. Koch, C. *The Quest for Consciousness: A Neurobiological Approach*. Roberts and Co., 2004.
3. Hargittai, I.; Hargittai, M. *In Our Own Image: Personal Symmetry in Discovery*. Kluwer/Plenum, New York, 2000.
4. Crick, F. *What Mad Pursuit: A Personal View of Scientific Discovery*. Basic Books, 1988, pp. 49–51.
5. Hargittai, I. *The Road to Stockholm: Nobel Prizes, Science, and Scientists*. Oxford University Press, 2002.

6. Hargittai, M.; Hargittai, I. *Candid Science IV: Conversations with Famous Physicists*. Imperial College Press, London, 2004, pp. 272–285. Penzias was co-discoverer of the residual heat in the Universe that gave proof for Gamow’s Big Bang theory of the origin of the Universe. Penzias became a Nobel laureate whereas Gamow never received this award.
7. Hargittai, B.; Hargittai, I. *Candid Science V: Conversations with Famous Scientists*. Imperial College Press, London, 2005.