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Preface

In the spring of 1953 at the Cavendish Laboratory, Cambridge, James Watson and Francis Crick presented a model of the structure of DNA. This glimpse of the gene that lent Watson and Crick such historic status marked the founding of molecular biology, a discipline characterized by the integration of biochemistry and genetics that has since dominated much of modern biology. The years following are often referred to as a "golden age," an era comparable in impact to the revolution in physics that transpired earlier in the 20th century.

Sydney Brenner, an enthusiastic and talented 22-year-old biologist from South Africa, was one of the earliest visitors to view the newly unveiled DNA structure. Brenner, then a graduate student in the Department of Physical Chemistry at Oxford, made a striking impression on Crick, who was determined to recruit the young South African to Cambridge. His efforts yielded extraordinary dividends. In the following years, the two deciphered many of the elements of gene function in a breathtaking series of contributions that surely marks one of the most creative periods in the history of biology. Their intellectual partnership dissolved when Brenner sought new research horizons and alighted on the nematode *Caenorhabditis elegans*, a tiny worm that became a celebrated model organism for probing the complexities of life in multicellular organisms. The 2002 Nobel Prize in Medicine or Physiology recognized the importance of this contribution.

Sydney Brenner is widely regarded as one of the leading molecular biologists of the twentieth century. But the effort of documenting his life is not restricted to recounting his contributions in the research laboratory. He was a significant influence in moderating the frenetic debates on recombinant DNA technology in the mid-1970s, and in helping to orchestrate Britain's involvement in the Human Genome Project in the early 1990s. And for about a decade he directed the Laboratory of Molecular Biology in Cambridge (which replaced the crowded and dilapidated Cavendish Laboratory) with its excellent scientific staff—many Nobel Laureates.

Rules established by the Medical Research Council in the United Kingdom required that Brenner formally retire as a paid scientist in 1992, when he reached the age of 65. But, at the time of this writing, Brenner is as active as ever scientifically, showing no signs of slowing down. In his later years he profoundly influenced the emergence of cutting-edge biomedical research in Singapore, one of the Asian tigers seeking to break into the front ranks of molecular biology and biotechnology. He has since inspired and lent his organizational skills to restructuring the sociology of molecular biology in Japan and to help guide the future of the Janelia Farm campus of the Howard Hughes Medical Institute. All these efforts were undertaken while Brenner actively continued to guide diverse scientific projects in other parts of the world and to promote efforts in the biotechnology sector.

Brenner's single-minded passion for biology has long dominated his waking—and presumably more than a few of his sleeping—hours, leaving him little time for other pursuits. But aside from his scientific contributions, which remain undiminished, Brenner possesses a broad intellect that embraces more than a superficial knowledge of the arts and history, and his talent as a raconteur is widely celebrated. He has dazzled, amused, and offended countless audiences with his wit and ironic humor; his iconoclastic views on ideas related to the exploration of life on this planet (and on planets yet unseen); and his general disdain of authority and dogma. He is, in fact, the proverbial enfant terrible.

An inveterate talker, Brenner can (and usually does) dominate any conversation of which he is part. But ironically, he is very much a loner, far preferring to think about and execute scientific experiments than to cavort with friends and acquaintances. As is evident among the photographs in this volume, he tends to set himself apart in group situations, and his countenance sometimes reflects the utter boredom associated with time away from the laboratory, the library, or his desk.

This biography begins with Brenner's humble beginnings as the child of an immigrant cobbler father and homemaker mother in the town of Germiston, South Africa. It then follows his educational path, from his years as a medical student at the University of the Witwatersrand in Johannesburg, South Africa, through his sojourn at Oxford University where he acquired a second doctoral degree, to his long association with Cambridge University and his wandering career as a "retired" scientist. Much of the book is based on information from personal interviews with Brenner and with a number of his former and current scientific associates, friends, and relatives. My efforts were also helped considerably by a 15-hour videotaped interview by

Lewis Wolpert in 1994, that I converted to a chronologically comprehensive text, entitled *Sydney Brenner: My Life in Science*, published in 2001 by BioMed Central. All unreferenced quotations from Brenner are from this source (regrettably now out of print). Readers should be aware that direct quotations from Brenner and others of British or British colonial origin use traditional English spelling. I have also quoted (accurately, I hope) from my interviews with others.

Sydney Brenner is among the very few key individuals to foster the early development of the discipline of molecular biology. Clearly history will determine how that period should be viewed in the context of preceding and succeeding events in the world of biology. This book therefore is neither offered as a definitive documentation of Sydney Brenner's life, nor as an attempt to establish his place in the annals of science. It is, rather, my hope that it will provide a useful foundation for more detailed and analytical contributions by future scholars and commentators.

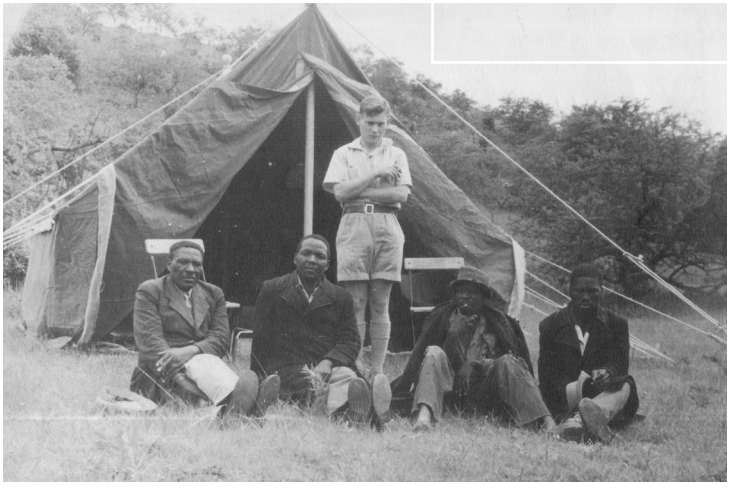
Evolution is a central topic among Sydney's many eclectic scientific interests. For this reason alone I am delighted that this work was essentially completed in 2009, a year that celebrates the 200th anniversary of the birth of Charles Darwin. Darwin and Gregor Mendel rank high on Brenner's very short list of scientific heroes.

ERROL C. FRIEDBERG
February 2010

Sydney Brenner receiving the Nobel Prize award from the King of Sweden, 2002. (Courtesy of Martin Chalfie.)

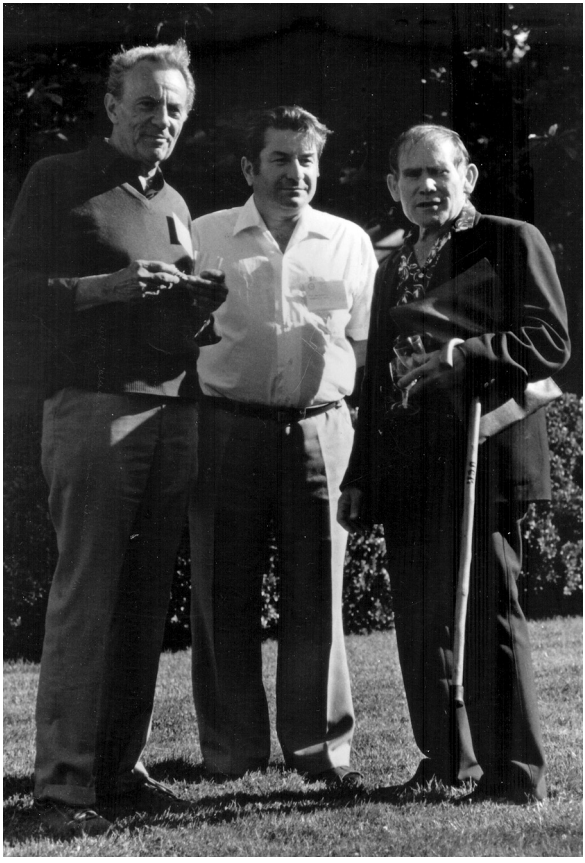
*The Brenner family, circa 1952. (*Left to right*) Maurice Finn, husband of Sydney's sister Phyllis, Sydney's father Morris Brenner, Sydney, his mother Leah Brenner, Phyllis Finn, and Sydney's younger brother Isaac (Joe). (Courtesy of Phyllis Finn.)*

*The Governing Board of the MRC Laboratory of Molecular Biology, 1967. (*Left to right*) Hugh Huxley, John Kendrew, Max Perutz, Francis Crick, Fred Sanger, and Sydney Brenner. (Courtesy of MRC Laboratory of Molecular Biology.)*



Brenner in the South African bush, circa 1945. (Courtesy of Sydney Brenner.)

*Brenner (*right front*) at the Cold Spring Harbor Laboratory Phage Meeting, 1954. Immediately behind him are (*left to right*) Al Hershey, Milislav Demerec, and Francis Crick. (Photograph by Norton Zinder, courtesy of the Cold Spring Harbor Laboratory Archives.)*



François Jacob, Max Bernstiel, and Brenner at the 1985 Cold Spring Harbor Symposium. (Courtesy of the Cold Spring Harbor Laboratory Archives.)

13

A Triplet Genetic Code

One of the most aesthetically elegant experiences of my life

Several years before the discovery of messenger RNA, soluble or transfer RNA (tRNA) was revealed to play a key role in protein synthesis. As we saw in Chapter 6, Francis Crick predicted the existence of this entity as early as 1955 in his theoretical paper On Degenerate Templates and the Adaptor Hypothesis, written for the RNA Tie Club. This treatise (which was never formally published) has been hailed by some as the finest example of theoretical biology in the 20th century and by Crick himself as his "most influential unpublished paper."[1] Not much later the Americans Paul Zamecnik and Mahlon Hoagland identified Crick's adaptors in the course of their studies on protein synthesis. They called this nucleic acid "soluble RNA," but by the early 1960s the more generally used term "transfer RNA" was adopted.

The essential mechanism of decoding genetic information and translating it to specific amino acids was now fully emerging: information for the assembly of a particular polypeptide encoded in DNA is first transcribed into messenger RNA. Once assembled at ribosomes, nucleotides in the messenger pair with complementary partners of individual transfer RNAs (each of which is charged with a cognate amino acid), resulting in the incorporation of amino acids in a specified order, to generate a unique polypeptide chain.

The stage was now set to decipher the genetic code, but crucial questions remained. How many nucleotides encode a single amino acid? What is the actual nucleotide code for each amino acid? Is the code script punctuated? What signals the beginning and end of the code in a gene? Perhaps most perplexing, why are there 64 possible triplet codons for only 20 amino acids?

As early as the mid-1950s, another RNA Tie Club communication, by Crick, Leslie Orgel, and John Griffith, presented the notion that the code

was comma-free, that is, functional groups of nucleotides (codons) are not punctuated.[a] Furthermore, as we saw in Chapter 7, Brenner had demonstrated the theoretical impossibility of an overlapping genetic code. However, by the early 1960s, progress with the so-called coding problem had been fitful and could be justly characterized as more conjectural than experimental.

Faced with these challenges Brenner and Crick revisited the issue. But the time for theorizing was over; the two now sought direct experimental evidence of how the code is read. As Crick candidly put it, "The time is rapidly approaching when the serious problem will be not whether, say, UUC is likely to stand for serine, but what evidence can we accept that establishes this beyond doubt."[2] During the course of a relatively brief period, in the early to mid-1960s, Brenner, Crick, and their respective colleagues—sometimes publishing together, sometimes independently—established the triplet nature of the genetic code. As we shall see in the next chapter, they also defined the distinction between "sense" and "nonsense" in the code and extended the notion of nonsense to explain polypeptide chain termination during normal protein synthesis. Brenner even identified some of the nucleotides that specify nonsense in the code by pure genetics—long before DNA sequencing was possible. Ultimately, he succeeded in his passionate quest to demonstrate colinearity between a gene and its polypeptide product, in a most unexpected and ingenious fashion.

These penetrating and rewarding contributions to molecular biology were wrought from the simple bacteriophage system by Brenner and Crick in the period between 1961 and 1965, a system requiring little more than Petri dishes, agar, pipettes, a few incubators—and two formidable scientific intellects. These efforts alone ought to have merited a Nobel Prize for Brenner and a second Nobel for Crick. During the decade of the sixties, many molecular biologists were honored as Nobel Laureates,[b] but these did not include Brenner, an oversight perplexing to many, including Sydney.

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[a] This theoretical study, entitled "Codes Without Commas," was formally published under the same title in 1957 (Crick FC, Griffith JS, Orgel LE. 1957. Codes without commas. *PNAS* **43:** 416–421). The authors presented an elegant theoretical analysis that led to the conclusion that only 20 codons specify sense, i.e., amino acids. The remainders are nonsense. Horace Judson referred to this contribution as "the most elegant biological theory ever to be proposed and proved wrong" (Judson, p. 315).

[b] The Nobel Laureates recognized for their contributions to the so-called golden age of molecular biology were James Watson, Francis Crick, Max Perutz, Maurice Wilkins (1962), François Jacob, André Lwoff, Jacques Monod (1965), Robert Holley, Gobind Khorana, Marshall Nirenberg (1968), Max Delbrück, Alfred Hershey, and Salvador Luria (1969).

It is difficult, if not impossible, to sort out the specific contributions of Crick and Brenner to their remarkable partnership. The pair enjoyed an intellectual complementarity that elevated their professional relationship to historic proportions. Crick liked to pursue ideas and hypotheses to their experimental conclusion, but he needed someone like Brenner to challenge him with new ideas. Brenner, on the other hand, required someone like Crick to filter his constant flow of ideas, many completely undeveloped at their inception. He was also less regimented than Crick and benefited greatly from the latter's discipline in bringing things to completion. "I think that had Francis Crick not existed I might have never written a paper in my life," Brenner stated. "It was Francis who made me write papers; because once I had solved a problem I lost interest in it. But Francis used to lock me in a room and say: 'You've got to write it up.' "[3]

Both men could talk endlessly and enthusiastically, and both loved to think aloud, preferably in the company of quick-minded, critical, and attentive listeners, such as each other. In Brenner's words: "Most of these conversations were just complete nonsense. But every now and then a half-formed idea would be taken up by the other one and really refined. I think a lot of the good things we produced came from these completely mad sessions."[4] Conversation, discussion, criticism, and argument were fundamental to their relationship, and they shared an office even when space in the new Laboratory of Molecular Biology obviated the need.

Brenner quickly discovered that Crick could be a very severe audience, one who challenged his colleague on poorly articulated ideas or suggestions. "One didn't get away with anything. He asked very penetrating questions and one had to be thinking all the time. But the clarification that came from this sort of dialog was very important." On a nearly daily basis, the pair spent hours exploring all manner of notions and ideas. Both scientists tended to be visual in their thinking and profited from drawing on the blackboards, especially to obtain a sense of the relative size and complexity of cellular and subcellular entities. "Francis was brilliant at visualizing molecular structure," Brenner related.

> He thought geometrically, like I do, not algebraically. Neither of us would sit down and write axioms and them proceed to deduce answers. We used diagrams a lot. Francis was very good at that too. But we were always careful to keep the scale of things in mind. That is very important. You see a lot of cartoons of a bacterium with a little circle inside to indicate the genome. But it's important to realize that there's a millimeter of DNA in that tiny bacterium! So Francis and I tried very hard to stay imprisoned in the physical context of everything.

Believing as he does that informed scientists sometimes unwittingly—sometimes wittingly—cultivate biases and prejudices about unsolved problems, Brenner likes to talk to intellectually stimulating scientists from other disciplines.

> I believe that people who come to a field from the outside, who have not been entrained to the standard approach, can sometimes see things from a different perspective. Gamow didn't know anything about molecular structure, but he saw things from the perspective of a physicist and he could pose problems in a form that no biochemist would or could.

Crick echoed these sentiments: "It was a blissful period because the problems were important,"[5] he wrote in a tribute to Brenner on the occasion of his colleague's 75th birthday.

> Only a few people (most of them friends) were working on them then and, thanks to the Medical Research Council's support, we didn't have to write grant requests and could study whatever we liked. Sydney and I had discussions almost every working day—using several large blackboards—but he also spent long hours in the lab and considerable time reading the literature.[c] He was much better than I at thinking up novel experiments. My role was more that of a critic and clarifier.[5]

Science writer Matt Ridley also documented the Crick-Brenner dynamic.

> The dialogue between Brenner and Crick was a conversation that developed its own rules. There was no shame in floating a stupid idea; but no umbrage was to be taken if the other person said it was stupid. Anyone else from the lab could walk in and interrupt if the door was open, but strangers were directed to see the secretary. Like Watson, Brenner knew a lot more biology than Crick. [On the other hand] Brenner found Crick an "incredible cross-examiner" who always challenged him on how to test an idea with a real experiment.[6]

Crick described his memory to his biographer Robert Olby as fallible, but offered the opinion that "Brenner has an amazing memory . . . he is a traveling encyclopedia on a cornucopia of subjects from medieval history to paleontology and computer science."[7] Crick further volunteered that his collaboration

---

[c] Both Benner and Crick read the literature voraciously. Matt Ridley commented: "Crick . . . was a ravenous consumer of others' results, from even the most obscure publications, and he had formidable powers of concentration. When Aaron Klug once asked why Crick was wasting time on a obviously useless paper the response was, '[T]here might be a clue in it' " (Ridley M. 2006. *Francis Crick: Discoverer of the Genetic Code*, p. 103. Eminent Lives Series, London).

with Brenner was not only fundamental to the development of ideas, "but it was all such fun. It says much for his tolerance and good temper that there was never an angry word between us. Happy days!"[8]

Crick had largely confined himself to a theoretical role in the hectic scramble to investigate the nature of the genetic code and its operation. However, he soon began carrying out experiments on phage mutagenesis with his own hands. He was then keenly interested in the problem of mutational suppression (sometimes referred to as mutational curing), a phenomenon in which a mutant phenotype is eliminated in the presence of a second mutation elsewhere in the genome. A particularly challenging example of mutational suppression surfaced from experiments carried out by Alice Orgel (Leslie Orgel's wife and a graduate student under Brenner's supervision). She demonstrated that the polycyclic aromatic dye proflavine, a known mutagen, cured mutations generated by the same compound, but had no effect on mutations induced by other mutagens, such as bromouracil.

Crick and Brenner tossed the notion of suppressor mutations back and forth. The pair reasonably hypothesized that if a single mutation affected the function of a protein, a second mutation in another gene that affected a different protein might compensate or suppress the phenotype of the first mutant. But they were disturbed by the huge number of suppressor mutations that Crick observed when phage was exposed to proflavine—more than could be comfortably accommodated by phenotypic suppression. Furthermore, Crick noted that, in every case, a proflavine-induced suppressor mutation mapped very close to the mutation it suppressed, suggesting that this mechanism was local rather than one acting at a distance.

As was Watson and Crick's tendency some years earlier, Brenner and Crick frequented The Eagle, a local pub well populated with Cambridge University types. While at the pub one Saturday morning, Brenner had another remarkable epiphany—no less sudden and providential than the messenger RNA insight that had emerged shortly before in his rooms at King's College.

> I suddenly had the notion that if, as people had suggested, the planar dye proflavine inserted itself between base pairs, one might have a situation where the DNA "thought" that the dye molecule was another base and the cell stuck in an extra base on the other strand during DNA replication, or made a compensating deletion during replication. So the idea emerged of a connection between mutations and base additions and deletions.

This notion was supported by the suggestion by Crick, Orgel, and John Griffith in 1955 that one could write commaless codes in which one reading

frame of nucleotide triplets made sense while in every other frame it was nonsense.

The following Monday Brenner and Crick began experiments to test this hypothesis. They showed that all known spontaneous phage host-range mutations could be reverted with base analogues such as the thymine analogue bromouracil. However, the great majority of spontaneous mutations in the *rII* gene were not revertible with base analogues. Furthermore, mutations generated by base analogues (such as bromouracil) were not observed when proflavine was used as the mutagen. Crick and Brenner produced another theoretical paper entitled The Theory of Mutagenesis,[d] another classic in theoretical biology. Here they proposed that, in addition to the well-known nucleotide substitution mutations—transitions and transversions—there was another category—addition and deletion mutations. *"Acridines act as mutagens because they cause the insertion or the deletion of a base pair,"* the authors noted (italics in original).

"One could start with a mutant arbitrarily called 'minus,' which was due to the loss of a base," Brenner explained. "All the mutations that suppressed this minus, such as those caused by proflavine, would be 'pluses' such that when you added a single 'plus' to a single 'minus' they would cancel out and the phenotype would no longer be mutant." Brenner and Crick soon realized that if they could prove this model they would be able to determine whether the code was, indeed, spelled out in sets of three nucleotides—as everyone had long believed. "All we had to do was to ask for any mutation that was revertible by proflavine, how many bases must be added or missing for the mutation to be suppressed, i.e., to restore the normal reading frame."

Brenner speaks nostalgically of these experiments as "a sort of apotheosis of a genetic analysis." Both he and Crick marveled at the fact that fundamental conclusions emerged from such technically simple experiments. Literally dozens of experiments could be carried out more or less simultaneously, with results available in a day or so. The observations were simply to score whether or not growth of the phage occurred. "From this pattern it seems mad that you could deduce the actual triplet nature of the genetic code." The English microbial geneticist William Hayes later referred to these results as "a masterpiece of genetic analysis."[9]

Crick carried out many of the plus and minus experiments with his own hands. Crick's efforts exasperated Muriel Wigby, an experienced technician

[d] Brenner S, Barnett L, Crick FHC, Orgel A. 1961. The theory of mutagenesis (editorial letter). *J Mol Biol* **3:** 121–124.

who joined the laboratory soon after Brenner arrived in Cambridge in 1957. She remained his assistant for over 30 years, breeding worms (see Chapter 15) and bacteriophage alongside a slew of LMB scientists who would become Nobel Prize winners. Whatever her opinions about Crick's intellect, Wigby was not impressed by Crick's technical abilities, accusing the man of being "terribly clumsy."[10]

Wigby worked beside Brenner and Crick long enough to comprehend their whims and foibles in the laboratory. She found Crick generally more difficult than Brenner, particularly his inclination to blame her when experiments failed.[e] "When Francis gave me an experiment to do and it didn't come out the way he expected he would insist that there must be something wrong with the way I had done it," she protested.[10] In contrast, Brenner rarely questioned her technical competence. "But when experiments didn't work and he became angry or frustrated, he would walk back and forth in the lab muttering and sometimes swearing—in Afrikaans."[10]

Brenner noted:

> An interesting thing about these experiments was that it was a real house of cards theory. You had to buy everything. You couldn't take one fact and let it stand by itself and say the rest could go. Everything was so interlocked. You had to buy the plus and minuses and you had to buy the triplet phase; all these went together. It was the whole that explained it and if you attacked any one part of it the entire thing fell apart. So it was an all or nothing theory. And it was very hard to communicate to people. However, this was one of the most beautiful, aesthetically elegant experiences of my life, in which, just by doing these little operations you landed up with a detailed description of the molecular structure of living matter.

Brenner and Crick published their observations on the triplet nature of the code in a landmark paper entitled General Nature of the Genetic Code for Proteins that laid bare some fundamental features of the triplet genetic code.[11]

---

[e] Crick's impatience (and sometimes incompetence) with wet bench research was also commented on by the biochemist Mahlon Hoagland, who worked with him on tRNA at the Cavendish. "We would do an experiment and get some variation in results that Francis felt obliged to analyze and ponder at length. I would assure him that the variations were very likely an error—we would not find them if we repeated the experiment. . . . He had an uncanny ability to analyze and criticize, in *detail*, the experiments of others, but at the bench he became mired in the day-to-day messiness and inconclusiveness." (Olby R. 2009. *Francis Crick: Hunter of life's secrets*, p. 267. Cold Spring Harbor University Press, Cold Spring Harbor, New York.)

> A group of three bases (or less likely, a multiple of three bases) codes one amino acid.
>
> The code is not of the overlapping type. . . .
>
> The sequence of the bases is read from a fixed starting point. This determines how the long sequences of bases are to be correctly read off as triplets. There are no special "commas" to show how to select the right triplets. If the starting point is displaced by one base, then the reading into triplets is displaced, and this becomes incorrect.
>
> The code is probably "degenerate"; that is, in general, one particular amino acid can be coded by one of several triplets of bases.[11]

General Nature of the Genetic Code for Proteins was rich in conclusions and conjecture but contained little of the mass of experimental data on which they were based. In fact, the complete experimental details of these studies were not published until 1967.[12] While thumbing through the massive final draft of the paper that would occupy 73 pages of the *Philosophical Transactions of the Royal Society*, Crick idly commented to Brenner that the two of them were likely the only individuals in the world who would read the published paper. They, therefore, plotted to insert within the manuscript a bogus literature citation, credited to a figure of historic prominence who had absolutely nothing to do with biology. After some discussion, the pair settled on referencing a personal communication from Leonardo da Vinci. Crick commented: "[O]ne (unknown) referee passed it without comment, but we had a phone call from the other referee, who asked, 'Who's this young Italian working in your lab?' So reluctantly we had to take it out."[13]

Not all the multiple suppression experiments obeyed the simple plus or minus rule. Rare exceptions emerged in the data set. Many scientists might dismiss these as fundamentally unimportant curiosities that a reluctant graduate student may sometime wish to explore; not Brenner and Crick. "For a long time we hung on to the 'don't worry hypothesis'—that sooner or later there'll be an explanation for them." About five years later, explanations derived from their own experimental observations did, indeed, emerge.

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