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Essay

Who discovered messenger RNA?

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The announcement of the discovery of messenger RNA (mRNA) and the cracking of the genetic code took place within weeks of each other in a climax of scientific excitement during the summer of 1961. Although mRNA is of decisive importance to our understanding of gene function, no Nobel Prize was awarded for its discovery. The large number of people involved, the complex nature of the results, and the tortuous path that was taken over half a century ago, all show that simple claims of priority may not reflect how science works.

On May 13, 1961, two articles appeared in *Nature*, authored by a total of nine people, including Sydney Brenner, François Jacob and Jim Watson, announcing the isolation of messenger RNA (mRNA) [1,2]. In the same month, François Jacob and Jacques Monod published a review in *Journal of Molecular Biology* in which they put mRNA into a theoretical context, arguing for its role in gene regulation [3]. Aside from the technical prowess involved, these papers were feats of the imagination, for they represented an entirely new way of thinking about gene function.

Although insight and hard thinking played a decisive role in developing this new view of life, this work built upon over a decade of research by many groups in the US and Europe as they attempted to unravel how the genetic message gets from DNA to produce proteins. We can reconstruct what happened in these years not only by studying the papers that were produced, but also by examining the reminiscences of those who were involved, both in their memoirs [4–8] and in oral histories [9], including talks by participants at the conference on the history of mRNA that took place in August 2014 as part of the Cold Spring Harbor Laboratory Genentech Center Conferences on the History of Molecular Biology and Biotechnology.

The acceptance of the genetic role of DNA began in 1944 with the publication of Avery, McLeod and McCarty's first paper on the identification of the 'transforming principle' in pneumococcal bacteria as DNA [10,11]. For much of the 1950s, the suggestion that DNA was the hereditary material in all organisms was accepted as a 'working hypothesis' but nothing more — as late as 1961 a paper in *Nature* left the door open to the possibility that genes were made of proteins, not DNA [12]. One of the continuous concerns throughout this period was that it remained unclear how genes functioned.

A key insight came in 1953, when Watson and Crick suggested that the sequence of bases on a DNA molecule contains 'genetical information' [13]. The issue then became how that information was turned into biological function — the nature of the genetic code and how it worked. The person initially responsible for focusing attention on this problem was the cosmologist George Gamow. In the summer of 1953, Gamow wrote to Watson and Crick, suggesting a model for how the genetic code might function, which involved proteins being synthesised on the DNA molecule itself [14].

Gamow's ingenious theoretical model was dismissed by Crick as a non-starter because he was convinced that protein synthesis did not directly involve chromosomal DNA, but instead took place in the cytoplasm and required RNA, although it was not at all clear how that process occurred, or what the form or the function of RNA was. This conviction was based on the work of Jean Brachet in Belgium and Torbjörn Caspersson in Sweden, who in the 1940s had reported that RNA was found primarily in the cytoplasm, where protein synthesis took place, and that RNA levels increased in cells that were actively synthesising proteins [15,16].

The first hypothesis about how RNA fitted into gene function came from the Paris laboratory of André Boivin, who had been one of the earliest and most visionary supporters of Avery's claim that DNA was the hereditary material. In 1947, Boivin published a French-language article with Roger Vendrely in *Experientia* outlining his view; the idea was pithily expressed by the editor's English-language summary: "the macromolecular desoxyribonucleic acids govern the building of macro-molecular ribonucleic acids, and, in turn, these control the production of cytoplasmic enzymes" [17].

In 1952, Alexander Dounce, of Rochester Medical School, proposed a biochemical model of how protein synthesis occurred on an RNA molecule, not on DNA [18]. Although the model was wrong, Dounce hypothesised that "the specific arrangement of amino acid residues in a given peptide chain is derived from the specific arrangement of nucleotide residues in a corresponding specific nucleic acid molecule" — the first description of what Crick later called the hypothesis of 'colinearity' between nucleic acids and proteins. The following year, Dounce refined his and Boivin's conception of the link between nucleic acids and proteins, describing it as 'deoxyribonucleic acid — ribonucleic acid — protein' [19].

This may look very similar to our modern understanding, but Dounce was not specifying the form, location or function of the RNA in this description. None of those things were yet known. Furthermore, Dounce's model was not based on the transfer of genetic information between the different kinds of molecule — that idea had yet to be invented by Watson and Crick — but instead on three-dimensional RNA templates. For Dounce, each amino acid had a physical relationship with the DNA and RNA bases, rather than the abstract informational link that we now understand. His model was strictly analogue.

Up until the middle of the 1950s, thinking about what was taking place in the cytoplasm during protein synthesis was blurred by lack of knowledge. Although RNA-rich structures called microsomal particles were identified in the cytoplasm in the 1950s, it was only in 1958 that they were baptised 'ribosomes', during informal discussions at a conference [20]. Ribosomal RNA was the only form of RNA that had been clearly identified, and it was quite possible that this was the RNA intermediary between DNA and proteins that so many scientists assumed existed. Above all, there was no good evidence

that any form of RNA existed without being bound up with a protein [21].

Crick's idea

In 1957, Francis Crick gave a talk at University College, London, as part of a Society of Experimental Biology symposium entitled 'The Biological Replication of Macromolecules' [22]. Published the next year, this lecture became famous for its description of what Crick called the central dogma, which outlined a hypothesis for the transfer of information inside the cell, and argued that it was not possible for information to be transferred from proteins to DNA. In an uncirculated 1956 document Crick drew a little diagram summarising his view (Figure 1; this was not included in the published version).

While it might look as though Crick was hypothesising the existence of mRNA, this was not the case. Like everyone else, he was still hobbled by the lack of understanding about the nature and function of the ribosome. Crick argued that the 'obvious' location for the cytoplasmic 'RNA template' that his hypothesis required was what were still called microsomal particles (that is, ribosomes). Crick assumed that each ribosome consisted of a common protein structure together with a unique sequence of RNA, which acted as a template for the synthesis of a particular protein. Crick's view was based partly on Mahlon Hoagland and Paul Zamecnik's discovery that during protein synthesis radiolabelled amino acids were initially found only in the ribosomes, strongly suggesting that amino acids had to pass through the ribosome to be combined into a protein [23]. It seemed likely that the RNA in the ribosome was the template upon which the protein was made.

To explain how each amino acid got to the ribosome, Crick hypothesised the existence of what he called 'the adaptor': a small, highly unstable set of RNA molecules that would bring each amino acid to the ribosome in order to allow the ribosome to make the protein. Unknown to either side, Hoagland and Zamecnik were simultaneously identifying such an RNA species, which eventually became known as transfer RNA [24].

As Crick explained, there had to be at least two kinds of RNA in the cytoplasm — what he called 'template

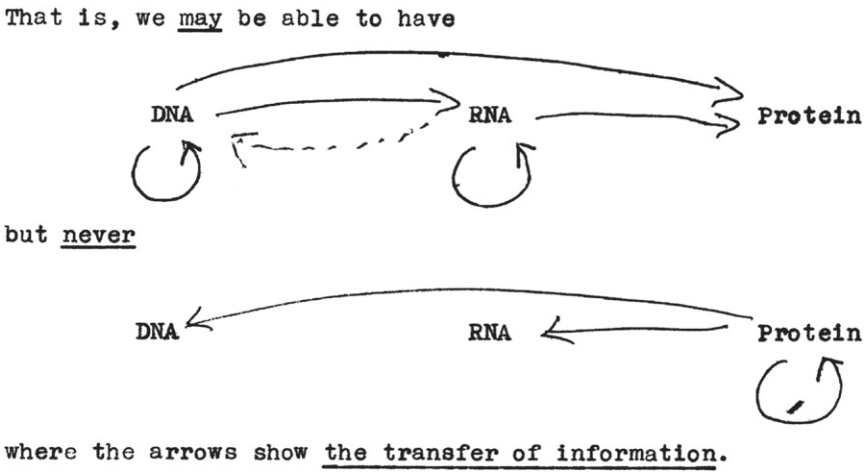

Figure 1. Francis Crick's unpublished 1956 sketch of the central dogma. (Image: Wellcome Library, London.)

RNA' located inside the ribosome, and 'metabolic' or 'soluble RNA', which he suspected was synthesised by each type of ribosome, and corresponded to the code on the template RNA. Neither of these kinds of RNA corresponded in form, function or location to what we now call mRNA, and even the brilliant mind of Francis Crick did not recognise the need for a third form of RNA.

Early sightings

In retrospect, a number of results from the 1950s indicated that there was a short-lived RNA intermediary produced by genes which we would now identify as being mRNA [25]. However, in each case either the speculative conclusions were not supported by the results, or the results were interpreted erroneously. In most cases, the articles are now remembered only by historians; there may be others that have yet to be rediscovered.

- In 1950, Jeener and Szafarz of the University of Brussels attempted to identify differential turnover in different RNA fractions, but were hampered by relatively primitive techniques. Nevertheless, they prophetically hypothesised that RNA was synthesised in the nucleus and then passed in the form of small molecules into the cytoplasm, where it was integrated with "cytoplasmic particles of large dimensions" before disappearing [26]. In 1958, Jeener showed that RNase prevented synthesis of phage proteins following infection of a bacterial cell and concluded that "RNA with a rapid turnover... is a specific product of the infection, and plays a role in the synthesis of phage protein" [27].
- In 1952 and 1954, first Monod's group [28] and then Arthur Pardee [29] showed that in mutant bacteria β-galactosidase synthesis required the presence of the RNA-specific nucleotide uracil, indicating that RNA synthesis was necessary for protein synthesis. Their conclusion — which was shared by Crick — was merely that this showed that at least some RNA in the cytoplasm showed turnover.
- In 1953, Al Hershey's group showed that shortly after infection with phage, bacteria produced a form of RNA that was both synthesised at a high level and also broken down rapidly. It was possible, however, that this was a pathological consequence of infection [30].
- In 1956, Elliot 'Ken' Volkin (Figure 2) and Lazarus Astrachan used radioactive phosphorus to show that when *Escherichia coli* cells were infected with bacteriophage, radioactivity was found in an RNA fraction, the base composition of which was very different from the RNA normally produced by *E. coli* [31]. However, their experiment did not reveal anything about the function of the RNA, and Volkin and Astrachan's preferred interpretation

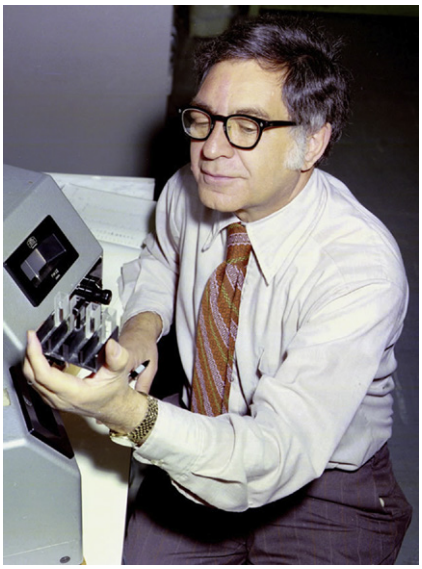

Figure 2. Ken Volkin, one of the first to observe mRNA. (Image courtesy of Oak Ridge National Laboratory, U.S. Dept. of Energy.)

was that this transitory form of RNA was a precursor to DNA.

- In 1958, Volkin and Astrachan found that while radioactive RNA appeared rapidly in bacteria after phage infection, if the isotope was added later, then more radioactivity was found in DNA than in RNA [32]. Their interpretation of these results again focused on how RNA might act as a precursor to the synthesis of DNA. Despite widespread interest in their results — Thomas Duke recalled that when they presented their findings at the 1956 FASEB meeting, the room was so packed he had to listen from the doorway [33], and in 1958 Volkin gave a talk at a conference session organized by Monod's group [9] — the interpretation of their finding as 'DNA-like RNA' obscured its true significance.
- Finally, in 1960, Nomura, Hall and Spiegelman refined Volkin and Astrachan's approach and showed that after phage infection two forms of RNA were synthesised: one was found in the ribosomal fraction, the other in soluble RNA [34]. They interpreted the soluble RNA fraction as either a precursor of ribosomal RNA (or its breakdown product) or as being involved in "the amino acid accepting function of normal soluble RNA", in other words something like Crick's adaptor molecule.

However, at the same time as Nomura *et al*. were putting the finishing touches to their paper, there was a breakthrough in thinking that led to the unambiguous identification of mRNA. This occurred during an informal discussion in Cambridge that has almost become legendary, as it reveals the role of sudden insight in some scientific discoveries.

Imagining mRNA

The realisation that genes produce a messenger molecule first occurred in Paris, during a sabbatical visit by Arthur Pardee to the Institut Pasteur, which began in 1957 [35]. Pardee was working with Jacques Monod on the genetic basis of induction, in which bacteria begin to synthesise β-galactosidase when reared on a medium containing lactose. Mutant *lac*– bacteria could not grow on lactose unless they acquired the z^+ gene, which coded for the β-galactosidase enzyme. Pardee showed that when the z^+ gene was transferred into a *lac*– individual, β-galactosidase synthesis began within minutes. This implied that there was an immediate chemical signal that passed directly from the introduced gene to the host cell's protein synthesis system. Over the next year or so, the Paris group became focused on the nature of this mysterious messenger molecule, which they called X (even amongst British and American scientists this was given the French pronunciation 'eex').

After the physicist-turned-biologist Leo Szilárd visited the Institut Pasteur in spring 1958, Pardee, Jacob and Monod began to consider that induction was not a positive effect, but rather what they called a 'de-repression' — in other words, β-galactosidase synthesis was normally repressed, but the presence of lactose somehow released that repression. Their findings became known as the PaJaMo (or, less precisely, PaJaMa) experiments, after the names of the three people involved. Following a sudden brainwave by Jacob in August 1958, the Paris team began to speculate that induction worked by directly acting on the repressor gene, either stopping its activity or inhibiting its product [36].

By the time they published the fullest version of their experiments and interpretation in 1959, they were calling the substance that acted on the repressor gene a 'cytoplasmic messenger'. But how exactly the process worked, and above all what the messenger was made of, they could not say.

Relations between the Insititut Pasteur and the Cambridge group around Crick and Brenner were cordial, but the two teams were working on rather different problems, so they rarely discussed their work informally. As Brenner later recalled, "You see, the Paris people were interested in regulation. We essentially were interested in the code. So we had a slightly different approach" [4]. Those two approaches finally collided on 15 April 1960, Good Friday, when a small group of researchers, including Crick and Jacob, gathered in Brenner's rooms in King's College, Cambridge, as a kind of informal 'after' meeting following a conference that had been held in London the previous day.

As the group chatted, Jacob explained the latest results from Paris, focusing on the puzzle of how the z^+ gene that enabled the cell to produce β-galactosidase was able to synthesise such high levels of the enzyme so soon after it was introduced into a cell. One of the possibilities that the Paris group had considered was that the gene coded for a very efficient type of ribosome, which then churned out the enzyme at a high rate. But, as Jacob explained, Pardee had recently done an experiment showing that the gene did not produce a stable ribosome, but only the transitory messenger molecule 'X'.

"At this point," recalled Crick, "Brenner let out a loud yelp — he had seen the answer" [5]. Jacob vividly described the following minutes:

> "Francis and Sydney leaped to their feet. Began to gesticulate. To argue at top speed in great agitation. A red-faced Francis. A Sydney with bristling eyebrows. The two talked at once, all but shouting. Each trying to anticipate the other. To explain to the other what had suddenly come to mind. All this at a clip that left my English far behind" [6].

In that moment, Brenner and Crick had realised that the mysterious PaJaMo messenger could explain the results from Volkin and Astrachan and others that suggested that following

phage infection, bacteria produced a short-lived form of RNA with the same base composition as phage DNA, and which differed from host ribosomal RNA. The two Cambridge men immediately seized on the possibility that this short-lived RNA was the mysterious Paris messenger. This would make the ribosome an inert structure in the cell — Crick described it as a reading head, like in a tape recorder.

Messenger RNA, as Jacob and Monod called it that autumn (this was soon abbreviated to mRNA), was like a tape that copied information from DNA and then carried that information to the ribosome, which read it off and followed the instructions to make the appropriate protein. This tape recorder metaphor can look rather quaint to 21st century eyes, and may need explaining to today's students, but at the time it was a cutting-edge analogy, using the latest technological developments to explain a new biological phenomenon.

Jacob and Brenner immediately began planning how to test the hypothesis. That evening, Crick and his wife held one of their many parties. Jacob recalled the scene clearly:

> "A very British evening with the cream of Cambridge, an abundance of pretty girls, various kinds of drink, and pop music. Sydney and I, however, were much too busy and excited to take an active part in the festivities…It was difficult to isolate ourselves at such a brilliant, lively gathering, with all the people crowding around us, talking, shouting, laughing, singing, dancing. Nevertheless, squeezed up next to a little table as though on a desert island, we went on, in the rhythm of our own excitement, discussing our new model and the preparations for experiment…A euphoric Sydney covered entire pages with calculations and diagrams. Sometimes Francis would stick his head in for a moment to explain what we had to do. From time to time, one of us would go off for drinks and sandwiches. Then our duet took off again" [6].

Isolating mRNA

Jacob and Brenner's proposed experiment required the help of Matt Meselson and his ultracentrifuges at Caltech in Pasadena. The challenge was to determine whether the messenger involved the creation of new ribosomes as Jacob and Monod had initially suspected, or instead consisted of a new transient form of RNA that simply employed the old host ribosomes to turn its message into protein. After a tense month in California, endlessly fiddling with the experimental conditions (the magnesium concentrations proved decisive), Jacob, Brenner and Meselson finally got the experiment to work. As they had hoped, no new ribosomes appeared; instead, a small, transient RNA that had been copied from the phage DNA was associated with old ribosomes that were already present in the bacterial host. This was messenger RNA.

Dramatic as this story is, it was not an essential step in the discovery of messenger RNA. Other researchers were independently taking a different route to the same conclusion, apparently with less excitement and fewer flashes of insight [8,21]. Their pathway to discovery shows that even if that Good Friday meeting of minds had never happened, mRNA would still have been isolated, probably on about the same timescale.

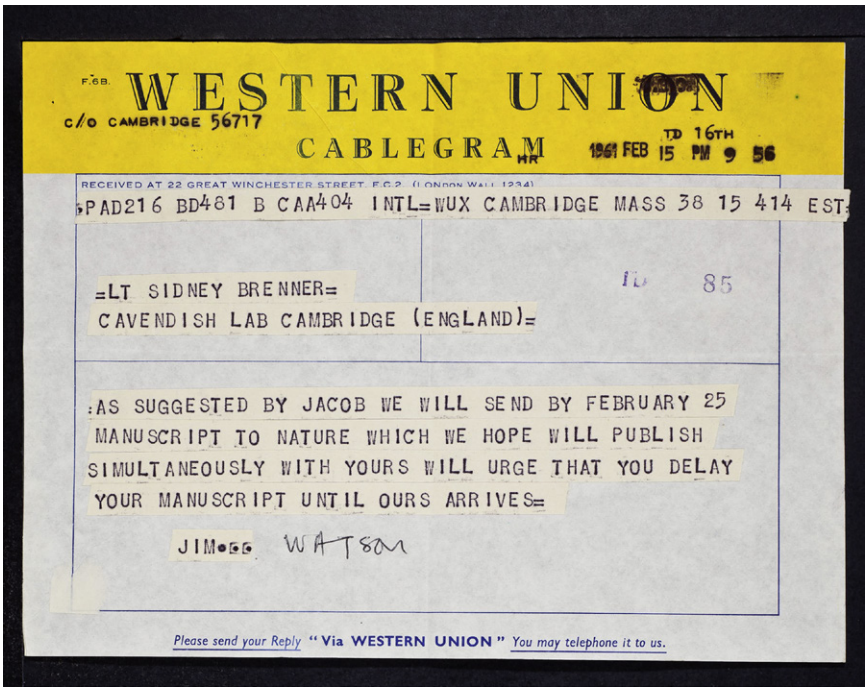

Figure 3. Telegram from Jim Watson to Sydney Brenner, 15 February 1961, requesting Brenner to delay publication of his article in *Nature* on mRNA until the Watson group's paper was ready. (Photo credit: Cold Spring Harbor Laboratory archives.)

Work by Robert Risebrough at Harvard convinced Jim Watson that protein synthesis took place through the action of transitory 'template' RNA molecules that were combined with 'genetically non-specific' ribosomes. Together with François Gros and Howard Hiatt of the Institut Pasteur, and Charles Kurland and Wally Gilbert from Harvard, Watson and Risebrough began a long series of experiments that revealed the presence of transitory RNA molecules in cells that were briefly exposed to a radiolabelled RNA precursor.

This took a great deal of time, and Watson's group was nearly scooped — Watson was furious when he heard that Brenner, Jacob and Meselson had submitted their paper to *Nature*, and in February 1961 he sent a telegram asking Brenner to withhold publication until the Watson group paper was ready (Figure 3). The trio generously agreed to Watson's request, and the two articles finally appeared back-to-back in May.

In the meantime, Jacob and Monod built on the unpublished results of the Brenner–Jacob–Meselson experiment

to codify the potential roles of what they termed 'messenger RNA' in a long review article, which was submitted in December 1960 [3]. This appeared in *Journal of Molecular Biology* in May 1961, at the same time as the two *Nature* articles.

In their dense but elegant and farseeing review, Jacob and Monod outlined their concept of structural and regulator genes, and then focused on the nature of 'X', the cytoplasmic messenger. On the basis of the wide range of evidence they reviewed — virtually all of it from studies of bacteria or bacteriophage — they came up with five criteria for the nature of the messenger: it was a polynucleotide; its molecular weight should vary from case to case; its base composition should reflect that of the DNA that produced it; it should at least temporarily be associated with ribosomes; and it should have a very high rate of turnover. Neither ribosomal RNA nor tRNA fitted the bill, but an excellent candidate appeared to be the transitory RNA reported by Volkin and Astrachan, and more recently by Yčas and Vincent in yeast [37]. Jacob and Monod called this RNA fraction messenger RNA, which they initially abbreviated as M-RNA.

The use of the term 'messenger' is significant, as it indicated that Jacob and Monod were not thinking in terms of an analogue, template molecule, but rather were beginning to view the problem in informational terms. The form of the message was not the key point — the essence they were highlighting was its meaning, or function.

At the beginning of December 1960, Sol Spiegelman and Benjamin Hall submitted an article to *PNAS* showing that in T2 phage, DNA and transitory RNA showed sequence complementarity and would hybridise [38]. The route for information to pass from DNA to RNA, first codified by Crick in 1957, had been shown to exist. The main conceptual components of gene function and protein synthesis were now in place. But no one had yet proved that the system actually worked.

Outsiders

Even before Jacob and Monod's paper was submitted, an obscure researcher at the National Institute of Arthritis and Metabolic Diseases in Bethesda was also thinking about messenger RNA. Marshall Nirenberg had obtained an MSc in caddisfly biology before changing subject and doing his PhD in biochemistry. After being turned down for a postdoc by Monod, Nirenberg eventually got a post at Bethesda, working with the charismatic jazz fanatic Gordon Tomkins, who at 35 years old was barely his senior.

Nirenberg initially studied induction, but following the development of 'cell-free' *in vitro* protein synthesis by Paul Zamecknik and by Severo Ochoa he turned his attention to the nature of protein synthesis and the genetic code. Nirenberg kept a remarkable series of laboratory diaries, in which he noted his ideas and aspirations. At the end of November 1960, Nirenberg's diaries were full of discussions about cell-free systems, the importance of messenger RNA, and the use of synthetic RNA as a key: "Can you swamp system with *messenger RNA*?" he wrote [39].

It is not clear where Nirenberg picked up this term — it had yet to be published, and the only paper that had been submitted using the phrase was the Brenner–Jacob–Meselon paper, of which Nirenberg seems to have been unaware [7]. Although Nirenberg was not part of the inner circle of molecular biology, the phrase 'messenger RNA' was being bandied about in conferences, so it is possible that he heard it either directly or through someone who had attended one of these meetings [40].

Whatever the case, it is clear that Nirenberg did not fully understand the three types of RNA that were being described by the researchers from Paris, Cambridge, Caltech and Harvard. As late as December 1960, Nirenberg's diaries show that he was still toying with the idea that protein synthesis took place on the DNA molecule, something most of the scientific community had abandoned years earlier [41].

In March 1961, Nirenberg and his post-doc, Heinrich Matthaei, submitted an article to the rapid-publication journal *Biochemical and Biophysical Research Communications* [42]. In this paper they described the output of their cell-free protein synthesis system, emphasising that what they termed ribosomal RNA and soluble RNA had to both be present for the experiment to work; soluble RNA on its own could not drive protein synthesis. An attempt to fractionate the ribosomal RNA suggested that the biological activity tracked to a fraction that sedimented about three times as fast as soluble RNA.

Similar-sized RNA molecules, attached to ribosomes, had been described at the beginning of 1961 by Aronson and McCarthy [43] but were interpreted as being either ribosomal precursors or breakdown products. Sharper, but still confused, Matthaei and Nirenberg concluded the discussion of their paper: "It is possible that part or all of the ribosomal RNA used in our study corresponds to template or messenger RNA". Despite the use of the term 'messenger RNA', this seems to imply that Nirenberg was still wondering whether ribosomes were the messenger — the very point that the Brenner-Jacob-Meselson experiment was designed to resolve.

It is striking that Nirenberg never cited this article (it has been cited only 14 times); the first person to cite it was Jim Watson, in his 1962 Nobel Prize address (he got the authors the wrong way round) [21]. Although it has been argued that this paper shows that Nirenberg was the first to isolate mRNA [41], neither the discussion nor the data justify this claim. Instead, the paper formed part of the complex of results and techniques that were coming to a head around the missing link in protein synthesis and gene function — messenger RNA.

As copies of *Nature* and *Journal of Molecular Biology* describing the nature and function of mRNA were arriving in letterboxes and libraries around the world, Heinrich Matthaei was carrying out the key experiment that would simultaneously read the first word of the genetic code and give a practical demonstration of the function of mRNA. He and Nirenberg had already shown that when tobacco mosaic virus RNA was added to their system, proteins were churned out at an amazing rate. Following a careful programme of experiments that had been laid out by Nirenberg over the previous months in his lab diaries, Matthaei

took the final step and showed that if a synthetic RNA molecule composed solely of uracil ('poly U') was added to the cell-free set-up, the system produced polyphenylalanine. The genetic code had been cracked — some combination of Us coded for phenylalanine.

This breakthrough from a couple of unknowns was first announced at the International Congress of Biochemistry held in Moscow in August 1961, and was then described by Nirenberg and Matthaei in *PNAS* in the early autumn [44,45]. Although this article again referred to 'messenger RNA' the confusion between ribosomal RNA and what we would call mRNA remained, and it did not refer to the poly(U) RNA in their experiment as functioning as mRNA. Further, they did not cite any of the three recently published papers that had first used the term mRNA (the two *Nature* papers and the Jacob and Monod review). Indeed, for reasons that remain obscure, Nirenberg never cited any of these three articles [7].

Nirenberg and Matthaei's revolutionary discovery utterly transformed how protein synthesis and the genetic code were investigated. When put together with the identification of mRNA, it represented a shift in our thinking about life that made perfect sense, once it had been understood. Those months in the middle of 1961 set the scene for everything that followed, changing our understanding forever.

Conclusion

Textbook authors, students and Wikipedia editors generally like simple stories. A simple view of the history of mRNA would claim that Jacob and Monod named it, while Brenner, Jacob and Meselson subsequently isolated it. The complexity of what actually took place is much more in keeping with what we know about science — a series of different groups attack a problem, using slightly different techniques, seeing the problem from different angles, before eventually a breakthrough makes clear what was previously problematic. From this point of view, priority of publication is not the sole criterion for contributing to discovery.

So the answer to the question 'who discovered mRNA?' depends on what you mean by 'discovered'. Many different groups have a claim, depending on which part of the mRNA story is being focussed upon:

- The first person to argue that DNA produces RNA which in turn leads to protein synthesis was André Boivin, in 1947.
- The first suggestion that small RNA molecules move from the nucleus to the cytoplasm and associate with ribosomes where they drive protein synthesis was made by Raymond Jeener, in 1950.
- The first reports of what we would now identify as mRNA were made by Al Hershey's group in 1953 and by Volkin and Astrachan in 1956.
- The realisation that mRNA might exist, with the functions we now ascribe to it, first came about through the insight of Brenner and Crick, while Jacob and Monod named mRNA and put it in a theoretical framework.
- The first unambiguous description of mRNA was jointly the work of Brenner, Crick and Meselson on the one hand, and of Watson's team on the other (although the Brenner–Crick–Meselon group got their results first).
- Finally, the first people to prove the function of mRNA were Nirenberg and Matthaei, although they did not frame their results in these terms.

Who discovered mRNA? It is complicated. No wonder the Nobel Prize committee did not try and reward the discovery. Naming just three (or even six) people would be invidious — mRNA was the product of years of work by a community of researchers, gathering different kinds of evidence to solve a problem that now looks obvious, but at the time was extremely difficult. But that is the nature of history — it straightens out what at the time was tangled and unclear. We have the advantage of looking backwards, knowing the answer; the participants were peering into a foggy future, trying to reconcile contradictory evidence and imagine new experiments that could resolve the problem. Their collective insights and imaginations laid the basis for today's understanding and tomorrow's discoveries.

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REFERENCES

1. Brenner, S., Jacob, F., and Meselson, M. (1961). An unstable intermediate carrying information from genes to ribosomes for protein synthesis. Nature *190*, 576–581.
2. Gros, F., Hiatt, H., Gilbert, W., Kurland, C.G., Risebrough, R.W., and Watson, J.D. (1961). Unstable ribonucleic acid revealed by pulse labelling of Escherichia coli. Nature *190*, 581–585.
3. Jacob, F. and Monod, J. (1961). Genetic regulatory mechanisms in the synthesis of proteins. J. Mol. Biol. *3*, 318–356.
4. Brenner, S. (2001). My Life in Science (London: BioMedCentral).
5. Crick, F. (1988). What Mad Pursuit: A Personal View of Scientific Discovery (Cambridge, Mass: Basic).
6. Jacob, F. (1988). The Statue Within (London: Unwin Hyman).
7. Judson, H.F. (1996). The Eighth Day of Creation: Makers of the Revolution in Biology (Plainview: Cold Spring Harbor Laboratory Press).
8. Gros, F. (1979). The messenger. In Origins of Molecular Biology: A Tribute to Jacques Monod, A. Lwoff and A. Ullmann eds, (London: Academic Press), pp. 117–124.
9. Volkin, E. (1995). What was the message? TIBS *20*, 206–209.
10. Avery, O.T., MacLeod, C.M., and McCarty, M. (1944). Studies on the chemical nature of the substance inducing transformation of pneumococcal types. Induction of transformation by a desoxyribosenucleic acid fraction isolated from pneumococcus type III. J. Exp. Med. *79*, 137–158.
11. Cobb, M. (2014). Oswald Avery, DNA, and the transformation of biology. Curr. Biol. *24*, R55– R60.
12. Eck, R.V. (1961). Non-randomness in amino-acid "alleles". Nature *191*, 1284–1285.
13. Watson, J.D., and Crick F.H.C. (1953). Genetical implications of the structure of deoxyribose nucleic acid. Nature *171*, 964–967.
14. Gamow, G. (1954). Possible relation between deoxyribonucleic acid and protein structure. Nature *173*, 318.
15. Brachet, J. (1942). La localisation des acides pentose nucléiques dans les tissus animaux et les oeufs d'amphibiens en voie de développement. Archi. Biol. *53*, 207–257.
16. Caspersson, T. (1947). The relations between nucleic acid and protein synthesis. Symp. Soc. Exp. Biol. *1*, 127–151.
17. Boivin, A., and Vendrely, R. (1947). Sur le role possible des deux acides nucléiques dans la cellule vivante. Experientia *3*, 32–34.
18. Dounce, A.L. (1952). Duplicating mechanism for peptide chain and nucleic acid synthesis'. Enzymologia *15*, 251–258.
19. Dounce, A.L. (1953). Nucleic acid template hypothesis. Nature *172*, 541.
20. Roberts, R.B. (ed) (1958). Microsomal Particles and Protein Synthesis (London: Pergamon).
21. Watson, J.D. (1963). Involvement of RNA in the synthesis of proteins. Science *140*, 17–26.
22. Crick, F.H.C. (1958). On protein synthesis. Symp. Soc. Exp. Biol. *12*, 138–163.
23. Hoagland, M.B., Zamecnik, P.C., and Stephenson, M.L. (1957). Intermediate reactions in protein biosynthesis. Biochim. Biophys. Acta *24*, 215–216.
24. Hoagland, M.B., Stephenson, M.L., Scott, J.F., Hecht, L.I., and Zamecnik, P. (1958). A soluble ribonucleic acid intermediate in protein synthesis. J. Biol. Chem. *231*, 241–257.

25. Thieffry, D. (1997). Contributions of the 'Rouge-Cloître group' to the notion of 'messenger RNA'. Hist. Phil. Life Sci. *19*, 89–111.
26. Jeener, R., and Szafarz, R. (1950). Relation between the rate of renewal and the intracellular localization of ribonucleic acid. Arch. Biochem. *26*, 54–67.
27. Jeener, R. (1958). The action of ribonuclease, thiouracil and azaguanine on the synthesis of phage proteins by an induced lysogenic bacterium. Biochim. Biophys. Acta *27*, 665–666.
28. Monod, J., Pappenheimer, A.M., and Cohen-Bazire, G. (1952). La cinétique de la biosynthèse de la beta-galactosidase chez E. coli considérée comme fonction de la croissance. Biochim. Biophys. Acta *9*, 648–660.
29. Pardee, A.B. (1954). Nucleic acid precursors and protein synthesis. Proc. Natl. Acad. Sci. USA *40*, 263–270.
30. Hershey, A.D., Dixon, J., and Chase, M. (1953). Nucleic acid economy in bacteria infected with bacteriophage T2. I. Purine and pyrimidine composition. J. Gen. Physiol. *37*, 1–23.
31. Volkin, E., and Astrachan, L. (1956). Phosphorous incorporation in Escherichia coli ribonucleic acid after infection with bacteriophage T2. Virology *2*, 149–161.
32. Astrachan, L., and Volkin, E. (1958). Properties of ribonucleic acid turnover in T2-infected Escherichia coli. Biochim. Biophys. Acta *29*, 536–544.
33. Jukes, T.H. (1977). Federation meetings. Nature *267*, 8.
34. Nomura, M., Hall, B.D., and Spiegelman, S. (1960). Characterization of RNA synthesized in Escherichia coli after bacteriophage T2 infection. J. Mol. Biol. *2*, 306–326.
35. Pardee, A.B. (2002). PaJaMas in Paris. TIGS *18*, 585–587.
36. Pardee, A.B., Jacob, F., and Monod, J. (1959). The genetic control and cytoplasmic expression of "inducibility" in the synthesis of β-galactosidase by E. coli. J. Mol. Biol. *1*, 165–178.
37. Yčas, M. and Vincent, W.S. (1960). A ribonucleic acid fraction from yeast related in composition to desoxyribonucleic acid. Proc. Natl. Acad. Sci. USA *46*, 804–811.
38. Hall, B.D., and Spiegelman, S. (1961). Sequence complementarity of T2-DNA and T2-specific RNA. Proc. Natl. Acad. Sci. USA *47,* 137–146.
39. Kay, L.E. (2000). Who Wrote the Book of Life? A History of the Genetic Code (Stanford: Stanford University Press).
40. Rheinberger, H.-J. (1997). Towards a History of Epistemic Things: Synthesizing Proteins in the Test Tube (Stanford: Stanford University Press).
41. Portugal, F.H. (2015). The Least Likely Man: Marshall Nirenberg and the Discovery of the Genetic Code (London: MIT Press).
42. Matthaei, H., and Nirenberg, M.W. (1961). The dependence of cell-free protein synthesis in E. coli upon RNA prepared from ribosomes. Biochem. Biophys. Res. Comm. *4*, 404–408.
43. Aronson, A.I., and McCarthy, B.J. (1961). Studies of E. coli ribosomal RNA and its degradation products. Biophys. J. *1*, 215–226.
44. Nirenberg, M.W., and Matthaei, J.H. (1961). The dependence of cell-free protein synthesis in E. coli upon naturally occurring or synthetic polyribonucleotides. Proc. Natl. Acad. Sci. USA *47*, 1588–1602.
45. Nirenberg, M. (2004). Historical review: Deciphering the genetic code – a personal account. Trends Biochem. Sci. *29*, 46–54.

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Matthew Cobb's book *Life's Greatest Secret: The Race to Crack the Genetic Code* is published by Profile in the UK, and by Basic Books in the USA.

Q & A

Jacobus (Koos) Boomsma

Jacobus J. Boomsma received his PhD from the Free University of Amsterdam. A five-year Huygens Fellowship by the Netherlands Organization for Scientific Research made him move to Utrecht, Oxford, and Cornell, until he took up permanent residence in Denmark as Associate Professor at the University of Aarhus (1990). Here, he initiated his fungus-growing ant program in Panama as Research Associate of the Smithsonian Tropical Research Institute and coordinated the first of two EU-Research Training Networks. The second of these substantiated after he had become a Full Professor at the University of Copenhagen (1999), where he founded the Centre for Social Evolution in 2005. He developed split sex-ratio theory and the life-time-commitment (monogamy) hypothesis for the evolution of eusocial caste differentiation and obligate multicellularity. He facilitated several empirical research programs on other eusocial model systems and discovered the ant Lasius neglectus*, which may become Europe's most abundant invasive pest ant during the 21st century. He served terms as President of the International Society for the Study of Social Insects (IUSSI) and Vice President of both the European Society for Evolutionary Biology (ESEB) and the Society for the Study of Evolution (SSE). He received an Alexander von Humboldt Research Award (2001) and an Honorary Doctorate from the University of Helsinki (2010).*

What drew you to your specific field of research? I was deeply interested in natural history as a child, but it was not until my third year at university that a field course in ecology convinced me that I had probably chosen the right academic discipline. And I might well have changed my mind had not my PhD work been about ants whose sex ratio investments offered an entry into the evolutionary study of social adaptation and reproductive conflict. These were topics in the then nascent field of behavioral and evolutionary ecology that has become one of the most explicitly hypothesis-driven branches of biology.

Which aspect of your field would you wish the general public knew more about? The general notion that there are fundamental principles of social evolution in nature and that we can only understand them by clarifying the forces that threaten to corrupt cooperation from within. This applies similarly to family life and inter-specific symbiosis, which can range from altruism and mutualism to parasitism. Every manifestation of natural cooperation that we observe today has somehow managed to avoid disintegration for sufficient time to become an evolutionarily stable social system within a specific ecological setting. It is humans that are the exception to this rule. Our cultural achievements are increasingly offering us more fulfilling lives than natural selection would allow, but we need to understand our animal cooperation heritage to appreciate when and why human nature limits further advances in the human condition rather than helping them along.

Why is studying ants particularly interesting? The ants evolved complex, social life without the assistance of culture and conquered the terrestrial world by sheer evolutionary innovation. There are more than 13,000 described species and no other eusocial lineage rivals them in diversity of life-styles. I remember watching ants as a school boy, and later becoming aware of their huge abundance in temperate grassland ecosystems during my MSc work. Further reading taught me that ant queens have sperm banks that last for decades at ambient temperatures, and that a Latin American ant lineage farms fungi for food. These themes have remained stimulating intellectual companions ever since and inspired much of the research on fungus-growing ants that brings me to Panama every year. Although collecting ant fungus farms can be messy for us researchers (see picture), the resilience of these colonies in rebuilding their gardens in artificial nests within a day is truly amazing.

