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Essay review

Thinking outside the black-box: The case of Marshall Nirenberg and Oswald Avery

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Life's greatest secret: The race to crack the genetic code, Matthew Cobb. Profile Books, New York (2015). pp. 434, hardcover, Price: £25, ISBN 978-1781251409

The least likely man: Marshal Nirenberg and the discovery of the genetic code, Frank H. Portugal. MIT Press, Boston (2015). pp. 200, hardcover, Price £19.95, ISBN: 9780262028479

Following the award-winning performance by the actress Nicole Kidman as the crystallographer Rosalind Franklin in Anna Ziegler's recent play *Photo 51* and the subsequent glowing reviews that the production received, there has been much renewed interest in the pages of the British press about the discovery of the structure of DNA. Central to the story is the eponymous X-ray image of B-form DNA taken by Franklin and her PhD student Raymond Gosling, which one broadsheet reviewer described as showing nothing less than 'life's essence' (Cavendish, 2015). I suspect however that, had he read this particular review, Matthew Cobb, Professor of Zoology at the University of Manchester and author of *Life's Greatest Secret* might have politely raised a questioning eyebrow.

For as Cobb pointed out in an article for *The Guardian* last year, while no-one would dispute that 'Photo 51' was certainly an important clue, this X-ray image alone was not sufficient to reveal the detailed structure of the molecule (Cobb, 2015). It was the quantitative crystallographic measurements made by Franklin and disclosed in a report to the Medical Research Council that allowed James Watson and Francis Crick to deduce that the DNA molecule was composed of not one but two chains, and moreover, that these chains ran in opposite directions. As a result, in April 1953, they published their famous paper in *Nature* proposing the double-helical structure of DNA – alongside papers by Franklin and Gosling (Franklin & Gosling, 1953), as well as Maurice Wilkins, A.R. Stokes and H.R. Wilkins (Wilkins, Stokes, & Wilson, 1953) on the structure of DNA – which contained one particular sentence made all the more memorable for its sense of historic understatement:

> It has not escaped our notice that the pairing we have postulated immediately suggests a possible copying mechanism for the genetic material' (Watson & Crick, 1953a, p.737).

Although the discovery of the double-helix explained how the molecule could make copies of itself, it was a far cry from being 'life's essence' and I suspect that Cobb would also gently take issue with science-writer Matt Ridley's assertion that the discovery of the double-helix was nothing less than 'life solved' (Ridley, 2006, p. 73). For while the double-helical structure explained how biological traits might be passed from one generation to the next, it gave little indication as to how the molecule might specify those traits in the first place. To address this question, *Life's Greatest Secret* redirects our gaze away from the glare and noise surrounding 'Photo 51' and the double helix to suggest that a second paper published by Watson and Crick a month later contained a far more significant sentence: 'it therefore seems likely that the precise sequence of the bases is the code which carries the genetical information' (Watson & Crick, 1953b, p.965).

As Cobb reminds us, the phrase 'biological information' and the notion of DNA as a 'code' are used routinely in classrooms and laboratories today, but at the time of Watson and Crick's second *Nature* paper they were highly novel concepts. The aim of his book is to explore their origins and show how our modern conception of the genetic code emerged through the interplay of molecular biology, information theory and cybernetics with particular focus on the period from roughly 1944 to 1968. What becomes very apparent through this approach is that, while the events described in *Photo 51* and in James Watson's famous memoir *The Double Helix*, were certainly important, they formed but a single episode in a much broader historical development, details of which have been eclipsed by the sense of triumphalism that has since built up around Watson and Crick's first paper.

One of the key developments from this period that Cobb describes is the publication in 1948 of *Cybernetics: or Control and Communication in the Animal and the Machine* by the MIT mathematician Norbert Wiener. From his work on anti-aircraft defences during World War II, Wiener had derived the insight that goal-directed systems, whether organic or machine, could be understood in terms of negative feedback loops that communicated information as a mathematically quantifiable entity based on

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probability. Building on the work of the Hungarian-American physicist Leo Szilard, he also established an inverse relationship between information and entropy, or the amount of disorder in a system.

Wiener's book popularised both the idea that information could be conceived as a quantifiable mathematical entity and the concept of systems that operated using negative feedback loops. This latter idea became particularly significant in biology thanks to its influence on the French scientists Jacques Monod and Francois Jacob and their American colleague Arthur Pardee in their studies on gene regulation in bacteria (Cobb, 2015, p.159; Pardee, Jacob, & Monod, 1959). In most accounts of the history of molecular biology, however, Wiener's book has been eclipsed by another more famous title, *What is Life?* published by the physicist Erwin Schrodinger in 1944 whilst in exile from the Nazis in Dublin. Despite criticisms about the accuracy of its content from eminent figures such as Linus Pauling and Max Perutz, Schrodinger's book was described by Stephen Jay Gould as ranking among 'the most important books in twentieth century biology' (Gould, 1985, p.25; Sarkar, 2013, p.101). According to the physicist Gunther Stent it was no less than an *Uncle Tom's Cabin* for molecular biology, acting as a call to arms for many scientists —among them Wilkins, Watson, Crick and George Gamow — to turn their attention and energies to the problem of the gene (Stent, 1968, p.392). Crick said that for him the attraction of the book was that it 'suggested that biological problems could be *thought* about in physical terms — and thus it gave the impression that exciting things in this field were not far off' (Judson, 1996, p.88, emphasis in original). But as Cobb is careful to point out, despite its references to the genetic molecule as a 'code-script', Schrodinger's book did not articulate in precise terms the concepts of genetic information or a genetic code as we understand them today; while it suggested that the gene must be a giant molecule capable of immense variation, it gave no suggestion as to what the chemical nature of this molecule might be.

That same year two other events occurred, which the Nobel-winning microbial geneticist Joshua Lederberg later identified as having had 'consequences that can be viewed, in a historical perspective, as having comparable import' (Lederberg, 2000, p.194). The first of these was the successful landing of Allied forces on the beaches of Normandy on 6th June; the second, perhaps less widely known outside the scientific community, was the demonstration by the US medical researcher Oswald Avery and his co-workers Colin MacLeod and Maclyn McCarty that nucleic acids were the carrier of genetic information (Avery, MacLeod, & McCarty, 1944). Specifically, these scientists were able to show that DNA was the molecule responsible for conferring the biological trait of virulence in pneumococcus by inducing the appearance of certain specific polysaccharides on the surface of the bacterium in a process known as transformation. At a time when their immense potential for structural variation made proteins the most likely candidate for the genetic material, Avery's suggestion that nucleic acids might be far more than just a monotonous string of repeating tetranucleotides incapable of conferring biological specificity, was a truly revolutionary — and to many, controversial — idea.

The DNA transformation work raised a new and important question: how could a nucleic acid direct the synthesis of a specific polysaccharide on the surface of the bacterial cell (Morange, 1998, p.36)? But Avery himself did not pursue that question, being keen that speculation as to how the gene might work not distract him from the immediate task of confirming its chemical nature: '[W]ith mechanisms I am not now concerned. One step at a time and the first step is, what is the chemical nature of the transforming principle? Someone else can work out the rest.' (Avery, 1943; as cited in Dubos, 1976, p.219). One such someone who was keen to 'work out the rest' was the cosmologist and theoretical physicist Gamow who, together with Watson formed a highly select group of scientists, whose aim was to promote theoretical discussions about how the genetic code might work. Boasting such luminaries of science as Richard Feynmann and Edward Teller, this group called itself 'the RNA-Tie Club,' and consisted of twenty members — one for each of the naturally occurring amino acids — each of whom wore a tie hand-embroidered with a single stranded RNA helix and a small badge denoting the three letter acronym of a particular amino acid. Ultimately, however, Cobb points out, it was not through the 'pencil chewing'of these theoreticians that the code was finally solved, but rather through the arduous and often frustrating grind of doing biochemistry at the lab bench.

One young researcher who played a particularly important role in this latter work was Marshal Nirenberg, the subject of *The Least Likely Man* by the biologist Franklin H. Portugal, formerly of the scientific staff at the National Institutes of Health and currently Clinical Associate Professor of Biology at the Catholic University of America. One of Portugal's aims in this book is to explain why Nirenberg, whom he described as 'the most famous person you have never heard of,' is not better known today (p.xiii). In contrast to such other leading figures in molecular biology as Watson, Portugal tells us that Nirenberg had shown no early academic promise. But after a career that had taken him from a Masters degree on research into caddis flies to doctoral research into sugar metabolism in cancer cells, he arrived at his laboratory at the National Institutes of Health (NIH) in Bethesda one October morning in 1968 to find that his team had hung a banner saying 'UUU are great' in celebration of the news that he had just been named a winner of Nobel Prize in Physiology or Medicine (p.123).

The banner was a reference to a series of experiments that Nirenberg and his post-doctoral fellow Heinrich Matthaei had carried out using artificially synthesized polyuracil (hence the U's) molecules. Addition of these RNA molecules to a cell free system had resulted in the synthesis of a polypeptide composed of repeats of the amino acid phenylalanine, a discovery which when presented by Nirenberg at the International Congress of Biochemistry in Moscow in 1961 brought his work to the attention of Crick and others who were involved in trying to solve the genetic code. Nirenberg thus went from being an unknown outsider whose application to attend the June 1961 Cold Spring Harbor meeting had been rejected by the elite of molecular biology — largely members of the RNA Tie Club — to being at the centre of efforts to crack the genetic code. Seven years later, following further experiments with his post-doctoral researcher Philip Leder which showed that three RNA bases were sufficient to specify a single amino acid, Nirenberg was jointly awarded the Nobel Prize along with Har Gobind Khorana and Robert W. Holley, for his role in the "interpretation of the genetic code and its function in protein synthesis" (The Nobel Prize in Physiology or Medicine 1968, 2014).[1]

In the introduction to *The Least Likely Man*, Portugal points out that the question of who solved the genetic code remains a contentious one to this day (p.xii). Part of the problem may be that posing the question in this way oversimplifies what was, in fact, a complex process. For instance, Nirenberg's discovery needs to be considered in relation to the work done by Crick and former medical student-turned-molecular biologist, Sydney Brenner using frameshift mutants in bacteriophage to establish the triplet nature of the code. Brenner and Crick appear to have differed in their

[1] Khorana's contribution to cracking the genetic code was to develop the techniques to synthesize RNA oligonucleotides of precisely determined sequences that enabled the speedy matching of nucleotide triplets to their cognate amino acids, and Holley discovered and sequenced the first transfer-RNA, (t-RNA), the molecules that effect the transformation of the genetic code into its protein alphabet.