

# 10 extraordinary papers

## Genetics

### The structure of DNA

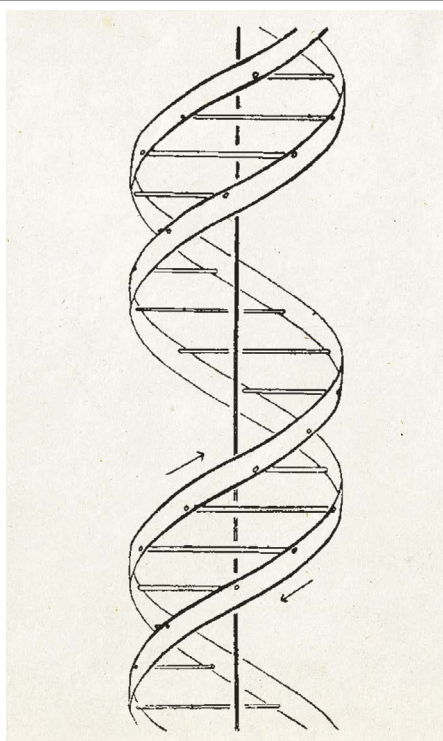
Georgina Ferry

In the early 1950s, the identity of genetic material was still a matter of debate. The discovery of the helical structure of double-stranded DNA settled the matter – and changed biology forever.

On 25 April 1953, James Watson and Francis Crick announced<sup>1</sup> in *Nature* that they “wish to suggest” a structure for DNA. In an article of just over a page, with one diagram (Fig. 1), they transformed the future of biology and gave the world an icon – the double helix. Recognizing at once that their structure suggested a “possible copying mechanism for the genetic material”, they kick-started a process that, over the following decade, would lead to the cracking of the genetic code and, 50 years later, to the complete sequence of the human genome.

Until that time, biologists had still to be convinced that the genetic material was indeed DNA; proteins seemed a better bet. Yet the evidence for DNA was already available. In 1944, the Canadian–US medical researcher Oswald Avery and his colleagues had shown<sup>2</sup> that the transfer of DNA from a virulent to a non-virulent strain of bacterium conferred virulence on the latter. And in 1952, the biologists Alfred Hershey and Martha Chase had published evidence<sup>3</sup> that phage viruses infect bacteria by injecting viral DNA.

Watson, a 23-year-old US geneticist, arrived at the Cavendish Laboratory at the University of Cambridge, UK, in autumn 1951. He was convinced that the nature of the gene was the key problem in biology, and that the key to the gene was DNA. The Cavendish was a physics lab, but also housed the Medical Research Council's Unit for Research on the Molecular Structure of Biological Systems, headed by chemist Max Perutz. Perutz's group was using X-ray crystallography to unravel the structures of the proteins haemoglobin and myoglobin. His team included a 35-year-old graduate student who had given up physics and retrained in biology, and who was much happier working out the theoretical implications of other people's results than doing experiments of his own: Francis Crick. In Crick, Watson found a ready ally in his DNA obsession.



**Figure 1 | The DNA double helix.** This drawing appeared in Watson and Crick's report<sup>1</sup> of the structure of DNA, and was produced by Crick's wife, Odile.

However, DNA was the project of Maurice Wilkins at King's College London. Crick was a friend of Wilkins's, and it wasn't the done thing for labs to compete over the same molecule. Moreover, the experienced X-ray crystallographer Rosalind Franklin had just taken over experimental work on DNA at King's. Owing to a misunderstanding about their relative roles, Franklin's relationship with Wilkins was frosty.

None of this stopped Watson and Crick from speculating about how the components of the DNA molecule – the four

nucleotide bases adenine, guanine, thymine and cytosine, connected to a backbone of sugars and phosphates – might assemble into fibres. They thought that a helix was a likely option: the US chemist Linus Pauling and his co-workers had just demonstrated<sup>4</sup> that peptide chains formed  $\alpha$ -helices. Crick himself had co-authored a paper on the theory of diffraction of X-rays by helices<sup>5</sup>. In late 1951, he and Watson combined that theory with what they knew about the chemistry of DNA, and what they remembered of talks given by Wilkins and Franklin, to build a model of the DNA structure.

They got it badly wrong: Wilkins and Franklin quickly demolished it. The head of the Cavendish, Lawrence Bragg, was furious, and banned Watson and Crick from doing any further work on DNA. But then, in February 1952, the Cavendish team received a manuscript from Pauling that contained a DNA model. It was wrong, but Watson and Crick were alarmed that Pauling was potentially near a solution.

This time, Bragg agreed that they might try to get there first. Franklin was soon to move to Birkbeck College, London, and was leaving the DNA work to Wilkins. She and her graduate student, Raymond Gosling, had given Wilkins a photograph of the X-ray-diffraction pattern produced by the B form of DNA. Watson went to see Wilkins, who showed him the photograph, without Franklin and Gosling's knowledge.

The now famous 'Photograph 51', together with other unpublished data of Franklin's that Perutz had shown Watson and Crick, told the pair that DNA did indeed form a helix, and that the structure consisted of two chains running in opposite directions. Watson was stumped, however, over how the bases could pair up between the two. He made cardboard cutouts of the bases, trying to fit them together, but nothing seemed to work.

His colleague Jerry Donohue then pointed out that he was using the molecular structures of the enol isomers of the bases, which cannot form the hydrogen bonds necessary for base-pairing. Once Watson had made cut-outs of the alternative keto isomers, he had the blinding revelation that when guanine bonded to cytosine, it made an identical shape to that of adenine bonded to thymine, and that the shapes fitted perfectly into the helical frame provided by the backbones of each DNA chain. This explained biochemist Erwin Chargaff's discovery that the DNA of any species has the same amount of guanine as of cytosine, and of adenine as of thymine<sup>6</sup>. It also showed that each DNA chain in a helix provides a perfect template for the other, reading the base sequence in opposite directions.

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Within days, Watson and Crick had built a new model of DNA from metal parts. Wilkins immediately accepted that it was correct. It was agreed between the two groups that they would publish three papers simultaneously in *Nature*, with the King's researchers commenting on the fit of Watson and Crick's structure to the experimental data, and Franklin and Gosling publishing Photograph 51 for the first time<sup>7,8</sup>.

The Cambridge pair acknowledged in their paper that they knew of "the general nature of the unpublished experimental results and ideas" of the King's workers, but it wasn't until *The Double Helix*, Watson's explosive account of the discovery, was published in 1968 that it became clear how they obtained access to those results. Franklin had died of cancer a decade previously; her death prevented her from sharing the Nobel prize awarded to Watson, Crick and Wilkins in 1962.

The immediate reception of the double-helix model was surprisingly muted<sup>9</sup>, perhaps because there was no obvious mechanism to explain its role in protein synthesis. In a landmark talk in 1957, Crick proposed that the base sequence encoded the sequence of amino acids in a protein, and that protein production involved RNA both as a template and as an 'adaptor' that would enable amino acids to be attached to one another in the right order. He also supported the suggestion – originally made informally by the physicist George Gamow to the members of the 'RNA Tie Club' convened by Gamow and Watson, but also independently proposed by biologist Sydney Brenner<sup>10</sup> – that triplets of bases (which Brenner called codons) encode the 20 amino acids commonly found in proteins. Finally, Crick expounded what he called the 'central dogma' of biology: that information can flow from nucleic acids to proteins, but not the other way round<sup>11</sup>.

These predictions were confirmed by experiment in the next few years. In 1958, the biochemists Matthew Meselson and Franklin Stahl showed that one DNA strand acts as a template for the formation of a new strand<sup>12</sup>. The same year, Arthur Kornberg and his colleagues published their discovery of the enzyme DNA polymerase<sup>13</sup>, which adds bases to newly forming strands. Messenger RNA, transfer RNA and ribosomal RNA were all quickly identified.

In 1961, Marshall Nirenberg and Heinrich Matthaei were the first to crack part of the genetic code, demonstrating that bacterial extracts synthesize only the amino acid phenylalanine from RNA that contains just one type of RNA base<sup>14</sup> (uracil; U). The same year, Crick, his indispensable female technician Leslie Barnett and their co-workers reported mutation studies that confirmed the existence of the triplet-based code<sup>15</sup>, and which therefore suggested that the codon for phenylalanine was UUU. The race to

identify the full set of codons was completed by 1966, with Har Gobind Khorana contributing the sequences of bases in several codons from his experiments with synthetic polynucleotides (see go.nature.com/2hebk3k).

With Fred Sanger and colleagues' publication<sup>16</sup> of an efficient method for sequencing DNA in 1977, the way was open for the complete reading of the genetic information in any species. The task was completed for the human genome by 2003, another milestone in the history of DNA.

Watson devoted most of the rest of his career to education and scientific administration as head of the Cold Spring Harbor Laboratory in Long Island, New York, and serving (briefly) as the first head of the US National Center for Human Genome Research, now the National Human Genome Research Institute. Always outspoken, he was eventually removed from his emeritus position at Cold Spring Harbor when he repeatedly aired controversial opinions about genetics, race and intelligence.

Crick continued to tackle hard problems in science, moving in 1977 from Cambridge to the Salk Institute in La Jolla, California, where he spent the rest of his life working on the neural basis of consciousness<sup>17</sup> and, specifically, of visual perception. He died in 2004, aged 88.

The double helix put genetics on a physical footing that would shed light on almost every aspect of modern biology and medicine. Examples include the migration of human populations throughout history; ecology and biodiversity; cancer-causing mutations in tumours and their drug treatment; surveillance of microbial drug resistance in hospitals and the global population; and the diagnosis and treatment of rare congenital diseases. DNA analysis has long been established

in forensics, and research into more-futuristic applications, such as DNA-based computing, is well advanced.

Paradoxically, Watson and Crick's iconic structure has also made it possible to recognize the shortcomings of the central dogma, with the discovery of small RNAs that can regulate gene expression, and of environmental factors that induce heritable epigenetic change. No doubt, the concept of the double helix will continue to underpin discoveries in biology for decades to come.

**Georgina Ferry** is a science writer based in Oxford, UK. A revised edition of her biography *Dorothy Crowfoot Hodgkin* has just been published by Bloomsbury Reader.

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### High-energy physics

## Detection of a strange particle

**Taku Yamanaka**

In 1947, scientists found a previously unseen particle, which is now called a neutral kaon. This work led to the discovery of elementary particles known as quarks, and ultimately to the establishment of the standard model of particle physics.

In the late 1940s, the physicists George Rochester and Clifford Butler<sup>1</sup> observed something unusual in their charged-particle detector. They were studying the interactions between high-energy cosmic rays and a lead plate in the detector when they spotted V-shaped particle tracks (Fig. 1a). The small

gap between the lead plate and the vertex of the tracks indicated that an invisible neutral particle had been produced in the plate, had travelled for a short distance and had then decayed into two visible charged particles. The mass of the neutral particle was about 1,000 times that of an electron, implying