

Great Discoveries in Science: The Double Helix

[JUDSON:] In the early twentieth century, physicists and chemists unlocked secrets of the atom that changed the world forever. But life remained a profound mystery. Among life's deepest secrets was inheritance. Everyone knew that traits like the shape of a peapod or the color of eyes and hair were passed on from generation to generation. But no one knew how such information was stored or transmitted. Scientists were convinced that there had to be a biological molecule at the heart of the process. And that molecule had to have some pretty special qualities.

[CARROLL:] The three dimensional arrangement of atoms in those molecules had to explain the stability of life, so that traits were passed faithfully from generation to generation, and also the mutability of life. You have to have change in order for evolution to happen.

[JUDSON:] The challenge of solving this mysterious arrangement of atoms, this fundamental "secret of life," was taken up in 1951 by two unknown scientists. Less than 18 months later, they would make one of the great discoveries of the twentieth century. They met and joined forces at the Cavendish laboratory in Cambridge, England. One was a 23-year-old American named James Watson.

[OLBY:] He had a crew cut when he first came to Cambridge, and that was very rare in Cambridge in those days. He liked to wear what I call gym shoes and leave the laces untied and things like that. He was quite an [^]enfant terrible[^] I would say. But behind that, of course, was his extreme, intense love of science right from his early years, and his determination.

[JUDSON:] The other was an Englishman named Francis Crick. Trained as a physicist, his academic career had been interrupted by the outbreak of the Second World War. It wasn't until 1949 that he got back into academic science. He was anxious to make up for lost time and now interested in biology. Crick and Watson connected instantly when they met in 1951. They both loved to talk science.

[WATSON:] Francis and I both liked ideas. And as long as I could talk to Francis, I, you know, felt every day was worthwhile.

[JUDSON:] Crick was always ready to share his thoughts, though he rarely did so quietly.

[WATSON:] Any room he was in he was going to make more noise than anyone else.

[LUGER:] They would constantly throw crazy ideas at each other, dismiss them, have another idea, follow that a little further, dismiss that, but then something comes out of left field, so it's kind of this give-and-take.

[CRICK:] We did have different backgrounds, but we had the same interests. We... we both thought that finding the structure of the gene was the key problem.

[JUDSON:] The idea of the gene dates back to Gregor Mendel's experiments with pea plants in the 1860s. By the 1920s, genes had been convincingly located inside the nucleus of cells, and associated with structures called chromosomes. It was also known that chromosomes are made of proteins, and a nucleic acid, deoxyribonucleic acid, or DNA. That meant that genes had to be made of either DNA or protein. But which was it? Protein seemed the better bet. There are lots of different kinds of them and they do lots of different stuff inside the cell. In contrast, DNA didn't seem very interesting. It's just repeated units of a sugar linked to a phosphate and any of four bases. The readiness to dismiss DNA was so entrenched that it persisted even after Oswald Avery showed that it can carry genetic information.

[CARROLL:] Avery had isolated a substance that conveyed a trait from one bacterium to another. And this "transforming principle," as he called it, he showed that it was not destroyed by a protein-digesting enzyme but was destroyed by a DNA-digesting enzyme.

[JUDSON:] Watson and Crick were among the few who found Avery's work persuasive. They thought genes were made of DNA. They also thought that solving the molecular structure of the molecule would reveal how genetic information is stored and passed on. At the time, a powerful technique for solving molecular structure was being perfected: x-ray crystallography.

[LUGER:] At its best, x-ray crystallography can determine the position of every single atom in the molecule that you're analyzing with respect to every other single atom.

[JUDSON:] Not that it's easy. The picture you end up with is a "diffraction pattern," and to make sense of it--to work out where the atoms are-- involves interpreting lengthy calculations. And in the 1950s, the equipment was primitive and difficult to maintain. The x-ray sources weren't very bright. And on top of that, DNA is not an easy molecule to work with.

[LUGER:] Basically, you picture snot. It's kind of hard to pick it up and do stuff with it, and analyze it. Polymers are not fun to work with from that point of view.

[JUDSON:] The Cavendish was famous for x-ray crystallography. But the director of the lab didn't want his staff x-raying DNA. He knew that a group at King's College in London was already doing that and he didn't want to be seen as competing.

[WATSON:] It just wasn't... good manners.

[JUDSON:] The King's College scientist who had initiated the work on DNA was Maurice Wilkins. Like Crick, he was trained as a physicist and had only recently become interested in biological questions. Though he was drawn to the problem of the gene, Wilkins lacked Watson and Crick's burning urgency to find a solution. Complicating things for Wilkins was his relationship with his colleague Rosalind Franklin. She was a talented

crystallographer, but when she joined the team at Kings she believed that she would be leading its DNA research.

[LUGER:] She had the notion that this was her project, he had the notion it was his project, and if anything, she should help him in his effort to solve the structure, and so this is a recipe for disaster.

[JUDSON:] The times and their personalities worked against an effective partnership.

[LUGER:] This was a time when it was very, very hard for women in science to be taken seriously and so I would imagine that Rosalind Franklin had to be perhaps quite assertive.

[JUDSON:] She certainly asserted her independence. Wilkins, by all accounts a shy man, reluctantly agreed that they would work separately. London is only 75 miles from Cambridge. That means that Watson and Crick could easily keep tabs on the work being done at Kings. But another potential competitor was thousands of miles away, in California. Linus Pauling was renowned as the greatest physical chemist of his generation. He was widely admired for his ability to build accurate models of complex molecules. Watson and Crick were convinced it was just a matter of time before Pauling used this technique to solve DNA. Biological molecules come in a variety of shapes. Pauling, and Watson and Crick, suspected DNA might be a helix of some kind. But if so, how were the sugar, the phosphate and the bases arranged? Early in his collaboration with Watson, Crick had worked out mathematically what the x-ray diffraction pattern of a helical molecule should look like. Shortly afterwards, Watson went to London to hear Franklin report on some of her recent work. When he got back, he told Crick what he remembered of her talk, and they decided to build a model. In a few days, they had one. It was a helix, with three sugar-phosphate chains on the inside, and the bases sticking out.

[LUGER:] At that time the only interesting thing about the DNA molecule is the bases. And so it made perfect sense, I mean, only an idiot would put them inside because then they're hidden.

[JUDSON:] They invited Wilkins and Franklin to come and take a look. Unfortunately, Watson had misremembered some of her key measurements. Franklin saw this immediately, and quickly and derisively dismissed their effort. She went to craft a mocking announcement for the death of DNA as a helix. It was an embarrassment that did not sit well with the Cavendish leadership.

[WATSON:] We were forbidden in a sense to work on DNA.

[JUDSON:] The failure of the first model was painful, but it can also be seen as just part of the scientific process.

[LUGER:] I would actually maintain that, in order to arrive at the right solution, you have to put out a couple of wrong ones. And that's just the nature of discovery, and if you're afraid of making a mistake, you're going to fail in this business.

[JUDSON:] Through 1952, Watson and Crick read and talked over anything and everything that could prove relevant for their ongoing-- but now underground-- quest to discover the structure of DNA.

[WATSON:] To me there was only one way I could be happy... or two ways, you know: solve DNA or get a girlfriend... [laughs] and I didn't get a girlfriend, so it was solve DNA.

[JUDSON:] The year ended with Watson and Crick thinking about DNA, Franklin taking pictures of DNA, Wilkins avoiding Franklin, and Pauling a distant but worrisome presence. Then, in January 1953, everything changed. News came that Pauling was indeed preparing a paper on the structure of DNA. Watson secured a copy of the manuscript. And found, to his great relief, that Pauling was proposing a triple helix. It was very similar to the one that he and Crick had been shamed into abandoning the previous year. Relieved, he headed to London to share the news that the race for DNA wasn't over. Only to find that Rosalind Franklin wasn't particularly interested in what he had to say.

[OLBY:] Following his departure from Rosalind Franklin's room he encountered Wilkins, and Wilkins took him into his room and then took out of a drawer a picture which had been taken by Rosalind Franklin.

[JUDSON:] That picture would become one of the most famous images in all biology: Franklin's Photo 51. Jim Watson recognized the diffraction pattern immediately-- it was a helix. And based on this, Watson thought it might have just two chains: a double helix. About the same time, Francis Crick was shown a report on Franklin's work that included an observation on the symmetry of DNA. This led Crick to a crucial insight that Franklin had missed: the two backbones had to run in opposite directions. That led him to the conclusion that the sugar-phosphate backbones had to be on the outside with the bases inside. So Watson started to build models again. He experimented with pairing like-with-like: adenine with adenine, thymine with thymine, and so on. That would make each chain identical. Watson thought that could explain how genetic information is stored. He thought he had the solution. But then a Cambridge colleague told him that the bases could not pair with themselves in that way. And Crick pointed out that the model didn't take account of something else that was known about DNA. A few years earlier, another chemist interested in DNA, Erwin Chargaff, had reported a puzzling fact about the molecule.

[LUGER:] He analyzed the chemical composition of DNA in different species and what he found is that the amount of As, the base adenine, and the amount of base Ts, was always the same. And Gs and Cs were always the same.

[JUDSON:] But no one, including Chargaff, had figured out what those base ratios meant. With Chargaff's data in mind, Jim Watson went alone to the lab one Saturday morning and started playing with cardboard cutouts.

[WATSON:] I began moving them around. And I wanted an arrangement, you know, where I had a big and a small molecule, and, uh, so how did you do it? Somehow you had to form link bonds. So, here's an A and here's T, and I wanted this hydrogen to point directly at this nitrogen, so I had something like this. Oh! So then I went to the other pair and I wanted this nitrogen to point to this one. And it went like this. Whoa! They looked the same. And you can put one right on top of the other. [music plays] We knew we could just... even if we go up to the ceiling, we're building a tiny fraction of the molecule. Hundreds of millions of these base pairs in one molecule, all fitting into this wonderful symmetry which we saw the morning of February 28, 1953.

[JUDSON:] The model fit the measurements, both from the x-ray diffraction pictures and from Chargaff's data. But most important of all, the arrangement of the bases immediately revealed how DNA works.

[CRICK:] The key aspect of the structure was the complementary nature of the bases. If you had a big one on this side you had to have a particular small one on this side or vice-versa, and so on, all the way up. So it meant that you could easily make... by separating the two chains, you could then easily make a new complementary copy, by just obeying these pairing rules of which one went with what. And that solved in one blow the whole idea of how you replicate a gene.

[JUDSON:] The structure immediately revealed two things: how genetic information is stored, and how changes, or mutations, happen. The information is stored by the sequence of the bases. Mutations occur when the sequence is changed.

[WATSON:] It's a simpler and better answer than we'd ever dared hope for.

[CRICK:] I remember an occasion when Jim gave a talk-- it's true they gave him one or two drinks before dinner-- it was rather a short talk, because all he could say at the end was, "well, you see, it's so pretty, it's so pretty."

[WATSON:] I think everyone just took joy in it because the field needed it. But on the other hand, you know [laughs], the Biochemistry Department didn't invite us to give a seminar on it.

[CARROLL:] When the structure of the double helix was revealed, most biologists instantly recognized the power of the explanation before them. Here was this beautiful molecule that could explain both the stability of life over huge amounts of time and its mutability in evolution.

[JUDSON:] Their triumph was reported in the journal Nature. It made headlines around the world. And was celebrated nine years later with a Nobel Prize.

[LUGER:] That's kind of what every scientist dreams about: to make a discovery that has this kind of impact.

[CARROLL:] For biologists, the discovery of the double helix opened up a whole new world. It was a passport to all the mysteries of life, mysteries that biologists have been decoding ever since.