

[The Debate over DNA Replication Before the Meselson-Stahl Experiment \(1953–1957\)](#) ^[1]

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Between 1953 and 1957, before the Meselson-Stahl experiment verified semi-conservative replication of DNA, scientists debated how DNA replicated. In 1953, [James Watson](#) ^[3] and [Francis Crick](#) ^[4] proposed that DNA was composed of two helical strands that wound together in a coil. Their model suggested a replication mechanism, later termed semi-conservative replication, in which parental DNA strands separated and served as templates for the replication of new daughter strands. Many scientists, beginning with Max Delbrück, questioned Watson and Crick's model and suggested new theories for DNA replication. By 1957, three theories about DNA replication prevailed: semi-conservative, conservative, and dispersive replication. Then, Matthew Meselson and Franklin Stahl conducted the Meselson-Stahl experiment, which returned results that supported the semi-conservative theory of DNA replication. The collaboration among scientists that ultimately produced concrete evidence of the DNA replication mechanism furthered both theoretical and physical explanations of genetics and molecular biology, providing insight into how life develops, reproduces, and evolves.

In 1952, Alfred Hershey and Martha Chase, two researchers who studied genetics and viruses in the US, experimentally verified that DNA played a role in genetic function, while protein did not. In the experiment commonly called the Hershey-Chase experiment, Hershey and Chase studied bacteriophages, which are viruses that infect bacteria, because bacteriophages were made up of only DNA and protein. Hershey and Chase found that when bacteriophages infected bacteria, the genetic material that the viruses injected into the bacteria consisted of DNA, while the protein coat was left outside the cell. They concluded that DNA was genetic material. Hershey and Chases' findings transitioned genetics from studying the varied traits in organisms caused by abstract "genes" to studying the physical manifestation of [genes](#) ^[5] in the form of DNA. According to molecular biologist John Cairns many scientists were reluctant to accept that a relatively simple molecule like DNA could explain so much of biology. Following the Hershey-Chase experiment, much of the scientific community, especially the subset of scientists who studied bacteriophages, investigated the structure of DNA and DNA's genetic implications.

[James Watson](#) ^[3] and [Francis Crick](#) ^[4], scientists at the University of Cambridge in Cambridge, England, published their hypotheses on DNA structure in 1953. In their paper that was published in April of that year, Watson and Crick proposed a structure for DNA that differed substantially from other proposed structures at the time. Watson and Crick argued that DNA existed as two helical strands wound together like a coil or rope. They said that the parts of the DNA double helix that varied from molecule to molecule, called bases, pointed inside the molecule, while the backbone remained on the outside. Lastly, Watson and Crick described experimental evidence indicating that the two strands comprising DNA complemented each other. They stated that the bases on one strand of a DNA helix corresponded to the bases on the other strand. Therefore, one could infer which bases are on one strand by identifying the bases on the other. According to Watson and Crick, that suggested that DNA replicated using the bases on each strand as a template for new strands.

According to historian of science Frederic Lawrence Holmes, while many scientists accepted the Watson-Crick model for DNA, some scientists, particularly Max Delbrück, immediately questioned the model. Delbrück, a researcher from the phage group at the [California Institute of Technology](#) ^[6] Caltech in Pasadena, California, disputed the orientation of DNA strands suggested by Watson and Crick. Delbrück wrote to Watson in response to the DNA replication mechanism suggested in Watson and Crick's paper. Delbrück stated that, based on Watson and Crick's model, in order for the individual strands of DNA to act as templates during replication, the strands needed to separate. According to Delbrück, that separation was impossible based on the way Watson and Crick hypothesized DNA coiled. Delbrück suggested that DNA possessed an alternate replication state in which the strands spiraled around each other without twisting so that they could later separate. According to Holmes, Delbrück's reservations about the Watson-Crick model for DNA replication caused Watson to be uncertain about his and Crick's model.

Despite that uncertainty, Watson and Crick published a second paper in May 1953, in which they specifically addressed DNA replication. Watson and Crick outlined a model for DNA replication, later called semi-conservative replication. According to Watson and Crick, in preparation for DNA replication, the two strands of DNA first unwound and separated. Next, each DNA strand functioned as a template for a new DNA strand, with the bases on each parent strand dictating new bases on the new daughter strands. Therefore, following replication, one parent double helix produced two new daughter double helices. Each daughter double helix contained one new strand and one parental strand, which was conserved from the parent double helix.

Following Watson and Crick's second publication, Delbrück continued to dispute semi-conservative replication. At some point in 1953, Delbrück abandoned his positions on DNA coiling. Holmes attributes the cause for the abandonment to a lecture Watson gave in 1953 at the Cold Spring Harbor Symposium in Cold Spring Harbor, New York. During the lecture, Watson directly addressed and discounted Delbrück's coiling ideas, though he never directly mentioned Delbrück by name. After that lecture,

Delbrück abandoned his first model of DNA replication, but he remained skeptical about DNA's ability to unwind for replication, as proposed by Watson and Crick.

Delbrück suggested a new model of DNA replication in a 1954 article, a model later called dispersive DNA replication. Delbrück argued that if each strand of DNA potentially serves as a template for a new strand during replication, like the Watson and Crick model theorized, then there could only be three ways to separate the DNA strands. Those three methods, Delbrück claimed, were by pulling the strands apart vertically, unwinding the strands, or by breaking the strands into small pieces and later rejoining them. Delbrück claimed that the first two methods were unlikely for two different reasons. First, he argued that pulling the strands apart lengthwise would cause the two-coiled strands of the double helix to interlock. Second, he argued that unwinding the strands was too energy-intensive. Instead, Delbrück suggested that DNA strands broke apart into pieces at every half-turn of the helix to prevent interlocking when separating. He theorized that those small pieces separated into two strands, duplicated themselves, and then joined back together after duplication. According to Delbrück's dispersive replication model, replication yielded two daughter helices for every parent helix, but that each strand within the daughter helices consisted of alternating parental and daughter DNA. The parental DNA dispersed throughout the daughter DNA.

Delbrück further described how his model of DNA replication could be experimentally tested. Delbrück stated that if researchers tracked the individual strands of a parent helix of DNA before replication, then, according to dispersive replication, those parental strands would disperse throughout the newly formed helices after many replications. Conversely, if DNA replicated semi-conservatively as suggested by Watson and Crick, then completely unlabeled DNA strands would be present in the daughter helices after the second replication. By suggesting such a test for DNA replication, Delbrück was the first scientist to publically propose a method for experimentally determining the model of DNA replication.

Delbrück was not the only scientist to suggest an alternate DNA replication mechanism. After Delbrück developed his model in 1954, George Gamow, a physicist at the University of California, Berkeley, in Berkeley, California, suggested a way that the two strands of the DNA double helix formed a spiraling configuration before replication, which would allow the strands to easily separate and not break. However, when Gamow informed Delbrück of his idea, Delbrück rejected the idea because it was a different form of his old coiling hypothesis. Early in 1955, John R. Platt of the Physics Department at the [University of Chicago](#)^[7] in Chicago, Illinois, proposed a separating mechanism called transfer-twist. Platt's mechanism suggested that rather than unwinding the DNA strands at one end, the strands instead pulled apart at points within the coil so that the strands twisted apart on their own. While both Gamow and Platt proposed new theories for DNA replication, neither scientist proposed means of testing those theories.

As other researchers suggested new models, Watson tried to address the issues surrounding DNA replication. While working at Caltech from 1954 to 1955, Watson theorized two four-stranded DNA models. Both structures involved DNA bases facing outward with the backbones facing inward, so that the strands functioned as templates, but did not have to separate in order to replicate. Furthermore, Watson's four-stranded structures included DNA that existed as a ribbon, or spiral, rather than a wound helix. Watson later abandoned those models after the Meselson-Stahl experiment.

While many scientists discussed DNA replication theoretically, Gunther Stent, who studied physical chemistry in Copenhagen, Denmark, tried to develop tools to experimentally determine the method of DNA replication. Stent began researching ways to test theories about the general replication of [genes](#)^[5] in the early 1950s. However, after Delbrück suggested his model in 1954, Stent specifically focused on DNA replication. Stent researched isotope labeling. Isotopes, which are alternate, less-stable forms of elements, weigh different amounts than the stable versions of their respective elements. Those differences in weight are traceable using a machine called a mass spectrometer. At the time, scientists wanted to incorporate isotopes into DNA so they could use the isotopes as a label to distinguish isotope-incorporated DNA molecules from molecules with no isotopes. Because DNA contains many phosphorus atoms, Stent tried to use the heavy phosphorus isotope, phosphorus-32, to label DNA in bacteriophages. However, the isotope lacked stability, decayed rapidly, and therefore did not distribute well throughout DNA. Nevertheless, Stent continued to research phosphorus-32 labelling into 1955 and published his findings in July.

In 1954, Matthew Meselson, a graduate student studying chemistry at Caltech, began studying DNA replication. After discussing DNA replication with Delbrück at Caltech in 1954, Meselson began thinking of ways to test the model of DNA replication. Like Stent, Meselson proposed labelling DNA with isotopes. Meselson, however, suggested using heavy nitrogen isotopes instead of phosphorus. When Meselson suggested the idea to Stent in the Spring of 1954, Stent dismissed the idea, stating that nitrogen isotopes would not be detected well enough by a mass spectrometer. However, Meselson's ideas did not require a mass spectrometer. Meselson hypothesized a method for suspending DNA molecules in a dense solution to separate isotope-labeled DNA molecules from unlabeled DNA molecules using an ultracentrifuge, a machine that spins samples rapidly to separate their components. Meselson and Franklin Stahl, a graduate student at the University of Rochester in Rochester, New York, later developed that method, called density-gradient centrifugation, which they applied to studying DNA replication in the Meselson-Stahl experiment.

As Stent and Meselson focused on experimentally determining DNA replication, other scientists continued to grapple with the theoretical aspects of DNA replication. In the fall of 1955, Niels Arley, another scientist from Copenhagen, proposed that DNA could be replicated from a protein template. Based on Arley's model, a protein could form within DNA and develop its own code, which would later be copied to form new DNA, so the parental DNA strands did not have to separate, thus avoiding the unwinding problem suggested by Delbrück. Later, David Bloch at [Columbia University](#)^[8] in New York City, New York, suggested

a mechanism in which the DNA rotated in such a way that the bases faced outward, so that the DNA strands did not have to separate in order to serve as templates during replication.

Stent furthered studies on phosphorus labeling through late 1955 and early 1956 in an attempt to experimentally determine how DNA replicated. Phosphorus-32 decayed quickly, so it killed any bacteria harboring its DNA. As bacterial cells replicate their DNA, they divide, thereby producing more bacterial cells. If DNA replicated semi-conservatively, some daughter DNA would not have the phosphorus-32 label, and the cells containing that DNA would not die. On the other hand, in dispersive replication, all daughter DNA would contain some phosphorus-32 DNA, so all of the cells would die. Stent analyzed the death patterns of bacterial cells exposed to phosphorus-32 in an attempt to determine the DNA replication mechanism. Stent found some distribution of the phosphorus-32 label in daughter DNA helices, which indicated the presence of parental DNA. However, his findings were not conclusive enough to pinpoint the exact replication mechanism.

Prior to 1956, Stent theorized a model of DNA replication different from semi-conservative and dispersive replication. In Stent's method, which he later termed conservative replication, DNA replicated without any parental DNA being incorporated into the daughter double helix. In other words, all parts of the parental double helix were completely conserved, and none were passed down to the daughter DNA helix. In theory, for conservative replication, DNA strands did not have to unwind and separate.

In 1956, Cyrus Levinthal, a researcher at the [University of Michigan](#)^[9] in Ann Arbor, Michigan, attempted to study DNA replication by studying phosphorus labelling in bacteriophages. Unlike Stent, Levinthal did not use a mass spectrometer to examine differences in DNA containing phosphorus-32, but rather he examined the differing radioactivity of DNA molecules containing phosphorus-32. Phosphorus-32 is a radioactive isotope, meaning that it emits a special kind of high energy light, which can be measured. Levinthal analyzed phosphorus-32 distribution in bacteriophage DNA by examining [radiation](#)^[10]. However, like Stent, Levinthal was unable to draw specific conclusions from his results.

In the spring of 1956, Delbrück and Stent summarized the three prevailing theories about DNA replication and proposed experimental ways to test those theories. Delbrück and Stent presented a paper in June of 1956 that described, in general, three testable methods for DNA replication. The methods, whose names were coined by Stent, were conservative, semi-conservative, and dispersive replication. Each method differed in terms of how much parental DNA was passed down to the daughter DNA, and how much parental DNA was conserved in the original DNA double helix. In addition to summarizing theorized modes for DNA replication, Delbrück and Stent also described experimental tests that would provide evidence for each method. Previous studies had indicated that distribution of parental DNA potentially occurred after DNA replication. If that was the case, according to Delbrück and Stent, testing for the exact way in which DNA duplicated itself would be very difficult, because the distribution of parental DNA would not be attributable to a specific event. The paper by Delbrück and Stent illustrated the challenges facing scientists studying DNA replication.

Following Delbrück and Stents' paper, in 1957, Herbert Taylor of the Oak Ridge National Laboratory in Oak Ridge, Tennessee, found that chromosomes, which contain condensed DNA, replicated semi-conservatively. Taylor labeled chromosomes in *Vicia faba*, a type of bean, using phosphorus-32. He found that with each replication, one subunit of a chromosome was conserved, while the other was not. However, Taylor could not conclude that the DNA making up chromosomes also replicated semi-conservatively.

Later that year, Meselson and Stahl conducted the Meselson-Stahl experiment, which showed that DNA replicated semi-conservatively. Meselson and Stahl conducted their research at Caltech. Like Taylor, Meselson and Stahl did not study bacteriophages. Because bacteriophage DNA proved to be very delicate, the researchers worked with the DNA of the bacteria *Escherichia coli*. Meselson and Stahl labeled DNA with heavy nitrogen isotopes. They then allowed that labeled DNA to replicate for many generations. Finally, they separated the DNA using density gradient centrifugation, to examine the distribution of parental DNA. Meselson's and Stahl's findings conclusively demonstrated that DNA replicated in a semi-conservative fashion as originally suggested by Watson and Crick.

According to Holmes, the Meselson-Stahl experiment largely settled the debate surrounding DNA replication. By the mid-1960s, the scientific community accepted semi-conservative replication and the work of Meselson and Stahl. However, perhaps more important than any one experiment, Holmes claims, was that scientists determined how DNA replicated through an international collaborative effort that consisted of years of theorizing, experimenting, and questioning. Those efforts led to experimentally confirming semi-conservative DNA replication, which formed the foundation for modern genetics, molecular biology, [reproductive biology](#)^[11], and developmental biology.

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Subject

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