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The book starts in 1953, when James Watson[5] and Francis Crick suggested that DNA replicates in such a way that one strand of the parental DNA is conserved in the daughter DNA, a method later termed semi-conservative replication. The book ends with the 1957 to 1958 experiment performed by Matthew Meselson and Franklin Stahl, called the Meselson-Stahl experiment. The question about DNA replication that Holmes writes about in his book arose from disputes surrounding the Watson-Crick model for DNA. In 1953, Watson and Crick, two researchers at the University of Cambridge in Cambridge, England, published an article on the structure of DNA as genetic material. That structure, called the Watson-Crick model, consisted of two complementary, or corresponding, helical strands of DNA wound around each other. As Watson, Crick, and other scientists at the time concluded, the complementary structure revealed a potential self-replication mechanism in which one strand of DNA served as a template for another, newly-replicated strand of DNA. The self-replication mechanism proposed by Watson and Crick, later termed semi-conservative replication, involved the two strands of DNA unwinding and separating, so that two new DNA strands would build off of the old ones. Therefore, two DNA molecules were made from one, and each new DNA molecule contained one old strand and one new strand.

After Watson and Crick's article was published, some scientists questioned semi-conservative replication and demanded that more research be done to determine its validity. In 1954, Max Delbrück, a scientist at the California Institute of Technology[6] (Caltech) in Pasadena, California, suggested a new model. Delbrück demanded experimental evidence to verify the method of DNA replication. After years of theorizing and experimental testing of different mechanisms of DNA replication, Meselson and Stahl conducted the Meselson-Stahl experiment from late 1957 to early 1958 at Caltech. The experiment provided evidence supporting semi-conservative replication of DNA.

In 1987, approximately thirty years after the Meselson-Stahl experiment, Holmes began working on his book. At the time of his book's writing and publication, Holmes was a professor at Yale University[4] in New Haven, Connecticut. In Replication of DNA, Holmes relied not only on scientific journal articles, interviews, and letter correspondence, but also on laboratory notebooks to capture the scientists' thought processes. The notebooks served to illustrate the daily activities of the scientist in preparation for and while performing different experiments. In Replication of DNA, Holmes presents diagrams, notes, and pictures from different laboratory notebooks. Including the time spent preparing his sources, Holmes spent twelve years writing his book on DNA replication.

Holmes structured Replication of DNA as third-person narrative with historical context and commentary intermixed throughout each chapter. After the "Preface," "Acknowledgements," and "Introduction," Holmes devotes fourteen chapters to recounting the DNA replication debate from 1953 to 1962. Although Meselson and Stahl are the focus of Replication of DNA, Holmes also discusses other scientists involved with the DNA replication debate. Chapter one provides context for the debate prior to Meselson's and Stahl's involvement. In chapter two, Holmes introduces Meselson and Stahl, as well as the two scientists' early work and initial collaboration. Chapters three through nine deal with events leading up to the Meselson-Stahl experiment. Then, in chapter ten, Holmes details the experiment. Holmes discusses the immediate and long term impacts of the Meselson-Stahl experiment in chapters eleven through thirteen. Lastly, Holmes concludes his book in chapter fourteen, followed by the "Abbreviations Used in Notes," "Notes," and "Index" sections, totaling the book at 503 pages.

In the "Preface" and "Acknowledgements" sections, Holmes introduces the significance of the Meselson-Stahl experiment, states his purpose for writing Replication of DNA, and identifies those who helped him write the book. In the "Preface," Holmes details the significance of the Meselson-Stahl experiment as a model experiment in the field of biology. Holmes cites the scientist, John Cairns, who described the Meselson-Stahl experiment as beautiful. Holmes continues by saying that while scientists considered the Meselson-Stahl experiment beautiful for its simplicity, its simplicity stems from the complex questions...
surrounding DNA replication. Holmes states in the "Preface" that the purpose of *Replication of DNA* is to illustrate the simple experiment in the face of its less than-simple origins. Holmes follows the "Preface" with an "Acknowledgements" section, in which he thanks the people who helped him as he wrote the book, including Meselson and Stahl, who participated in many interviews and read many drafts prior to the book's publication.

In the following section of *Replication of DNA*, "Introduction," Holmes discusses the significance of the Meselson-Stahl experiment, the purpose of the book, the overall structure, and his general approach to writing the narrative. When summarizing the debate about DNA replication, Holmes states that while many scientists attempted to answer questions about DNA replication, none were truly successful until Meselson and Stahl conducted their experiment. Holmes then addresses his intent as a historian, which was to connect the scientists' inner thoughts and inquiry to the experiments they performed. He states that his goal was to structure the narrative in such a way that it played out like a drama, with each scientist acting as a character.

In chapter one, "The Replication Problem," Holmes shows how Watson, Delbrück, and Gunther Stent, a scientist from Copenhagen, Denmark, initially involved themselves with the topic of DNA replication. After describing the 1953 DNA articles by Watson and Crick, Holmes introduces Delbrück's early reservations about the model through an analysis of the letters sent between Delbrück and Watson. By comparing Watson's later articles to his earlier ones, Holmes shows how Delbrück's early lack of support for the Watson-Crick model lead to Watson's growing apprehensions about his own model. Holmes also reveals how the sharing of ideas between Delbrück and Watson influenced Delbrück's views before Delbrück published his own article proposing a new model for DNA replication in 1954. In Delbrück's model, later called dispersive replication, pieces of each DNA strand broke apart, replicated, and rejoined. Holmes describes Delbrück's article as the start of the DNA replication debate. To end the chapter, Holmes discusses the early responses to Delbrück's article, including that of Stent, who approached DNA from an experimental standpoint. Holmes details Stent's early collaboration with Delbrück and Stent's mission to provide experimental methods to test the model of DNA replication. By the end of the first chapter, Holmes supplies the reader with the necessary information to understand the topic of DNA replication in the 1950s.

In the next chapter, "Meselson and Stahl," Holmes introduces Meselson and Stahl and describes how the two scientists first met. Holmes provides biographical information on the two scientists, as well as their career trajectories when the DNA replication debate started. Furthermore, Holmes describes the early developments of the Meselson-Stahl experiment. Those developments started with Meselson's ideas for density-gradient centrifugation, a method of separating molecules, which he later used with Stahl to perform the Meselson-Stahl experiment. Throughout the chapter, Holmes also tells of the first meeting between the two scientists. Meselson, a graduate student who studied chemistry at Caltech, and Stahl, a graduate student who studied biology at the University of Rochester in Rochester, New York, met during the summer of 1954 under a tree at the Marine Biological Laboratory in Woods Hole, Massachusetts. Holmes states that while sitting under that tree in Woods Hole, Meselson and Stahl agreed to study DNA replication together.

In the third chapter of *Replication of DNA*, "Twists and Turns," Holmes discusses Meselson, Stahl, and major developments in DNA replication in 1955 and 1956. Holmes continues to cover the scientific community's response to Delbrück's 1954 article by summarizing the many theories and experimental methods that arose to address questions about DNA replication, including individual contributions from Stent and Watson. Holmes emphasizes how Delbrück influenced the course of Watson's and Stent's research by serving as an inspiration and admired figure for them. As for Meselson and Stahl, who at the time worked separately while they finished their graduate work, Holmes contrasts the two student's personalities. While Holmes describes Meselson as carefree and enthusiastic with few social or financial struggles, Holmes writes that Stahl faced difficulties regarding both his finances and his marriage. Throughout *Replication of DNA*, Holmes points to how Meselson's and Stahl's difference in character pertains to each scientist's role in the Meselson-Stahl experiment, as well as their individual reflections on the time.

In contrast to the previous chapters, in chapter four, "Crossing Fields: Chemical Bonds to Biological Mutants," Holmes focuses on Meselson's daily activities. The events in "Crossing Fields" occurred during the summer of 1956. According to Holmes, Meselson spent many days in the library reading literature related to DNA so he could learn more about the subject. Holmes uses Meselson's old notebook to give a day-by-day account of Meselson's studies, which includes analyses of the articles Meselson read and descriptions of the different conclusions Meselson drew.

In the fifth chapter of *Replication of DNA*, "Dense Solutions," Holmes emphasizes both Meselson and Stahl and writes about the scientists' first collaboration at Caltech. As Holmes writes, Meselson and Stahl devoted much of their early collaborative work to develop the necessary steps of density-gradient centrifugation. Holmes writes about how Meselson's and Stahl's relationship influenced their personal career tracks. As Holmes states, Stahl, who moved to Caltech after finishing his graduate work, considered leaving Caltech for a different job in late 1956. However, according to Holmes, upon hearing the news of Stahl's potential move, Meselson convinced Stahl to stay so the two could find out how DNA replicated. Holmes writes that Meselson's and Stahl's first joint task was to find a solution dense enough to suspend DNA molecules in it. Such a solution was an integral part of Meselson's density-gradient centrifugation method to separate molecules, the idea of which he had thought of years prior. Meselson and Stahl discussed the problem over dinner and eventually hit upon a solution that would separate DNA molecules.

With Meselson's and Stahl's collaboration underway, Holmes devotes chapter six, "The Big Machine," to the scientists' research from October 1956 to November 1956. The majority of the chapter details how Meselson and Stahl obtained a special kind of ultracentrifuge that they needed to develop the method of density-gradient centrifugation. Holmes also devotes much of chapter
six, as well as the next two chapters, to the many other projects Meselson and Stahl worked on using density-gradient centrifugation. For chapter six, as well as all of the chapters involving experimentation to follow, Holmes relies on Meselson's lab notebook to detail Meselson's and Stahl's research.

In chapter seven, "Working at High Speed," Holmes continues to follow the daily laboratory activities of Meselson and Stahl established in chapter six. As Holmes writes, throughout the rest of 1956, Meselson and Stahl optimized density-gradient centrifugation so that other scientists could use the method for a suite of purposes. Holmes also furthers examines the other studies that Meselson and Stahl conducted that did not relate to DNA replication directly. Research proposals by Meselson and Stahl, which Holmes excerpts in his book, prioritized projects unrelated to DNA replication. Holmes states that when he showed one such proposal to Meselson, Meselson said that he never realized how much DNA replication had become a side project, rather than the main objective for him and Stahl during their collaboration. In later chapters, Holmes continues to analyze discrepancies between the scientists' memories and primary source documents.

Holmes returns to writing about DNA replication on a larger scale in chapter eight, "The Unseen Band." Holmes writes that while Meselson and Stahl developed density-gradient centrifugation and applied the method to other experiments, other scientists made progress on the DNA replication front. Holmes describes the early 1957 experiments by Herbert Taylor, a scientist at the Oak Ridge National Laboratory, which found that chromosomes, genetic material composed of condensed DNA, replicated semi-conservatively. Half of each chromosome was conserved after replication. However, according to Holmes, Taylor's experiment, as well as experiments by Stent and other scientists, did not provide conclusive evidence for the replication of DNA itself. Furthermore, Holmes states that those experiments did not completely discount other replication theories. Holmes writes that Meselson and Stahl re-prioritized DNA replication in 1957, but that the researchers experienced many pitfalls when trying to gather clear data. Despite the experimental difficulties, Holmes states that Meselson and Stahl continued to chiefly study DNA replication.

Chapter nine, "One Discovery, Three Stories," provides three historical accounts of Meselson's first major finding that DNA replicated semi-conservatively. Holmes states that while Stahl was out of state to interview for a job, Meselson conducted an experiment on his own which, to Meselson's recollection, provided the first promising evidence for semi-conservative DNA replication. However, as Holmes writes, even though Meselson regarded the findings as a major step forward in his experiment, his recollection of the event did not align with research notes. Meselson recalled a much greater breakthrough than the research logs suggested. In an attempt to provide a historical account, Holmes provides three possible stories: one completely based on Meselson's memory, one solely based on the research logs, and a hybrid of the two.

In chapter ten, "An Extremely Beautiful Experiment," Holmes details the Meselson-Stahl experiment as well as the experiment's immediate aftermath. Holmes writes that Meselson and Stahl conducted the experiment, later called the Meselson-Stahl experiment, from October 1957 to January 1958. As Holmes states, as soon as Meselson and Stahl received clear evidence that DNA replicated semi-conservatively, word spread quickly throughout the scientific community. Scientists such as Watson, Stent, and Delbrück, knew about the results before Meselson and Stahl published them. However, Delbrück remained cautious, as shown by letters written by Delbrück that Holmes includes in the chapter. According to Holmes, the Meselson-Stahl experiment provided substantial evidence that DNA replicated semi-conservatively, but did not reveal what particular subunits of DNA replicated in that fashion. Likewise, there was still a possibility that DNA did not exist as Watson and Crick originally predicted. It was possible that DNA existed as four strands, and each pair of strands replicated semi-conservatively. Holmes writes that while Meselson and Stahl felt that their results supported the Watson-Crick model for DNA, Meselson maintained some reservations for the same reasons as Delbrück. According to Holmes, Stahl attributed Meselson's caution to Meselson's scientific approach. Even though the Meselson-Stahl experiment ended the debate over DNA replication for many, the question of how DNA replicated was not entirely answered.

The eleventh chapter of Replication of DNA, "Centrifugal Forces," deals with the writing of Meselson's and Stahl's publication in 1958 as well as a detailed analysis of their article. According to Holmes, Meselson and Stahl resisted writing their article on their DNA replication results because each of them continued to conduct more experiments. Holmes provides an anecdote about Delbrück's effort to compel Meselson and Stahl to finish their article. According to Holmes, Delbrück drove the two scientists to Caltech's marine biological station in Corona del Mar, California, and forced them to work on their article for a few days in a tower overlooking the beach. As stated in an interview with Holmes, Meselson wanted to focus on the results of the experiment rather than the approach, and he wanted to avoid linking his and Stahl's findings to the Watson-Crick model of DNA.

In chapter twelve, "Subunits of Semiconservative Replication," Holmes writes about how scientists determined that the subunits of DNA were, in fact, single strands, thereby supporting the Watson-Crick model of DNA. Holmes states that some scientists still disputed the subunits of DNA until 1962, when Cairns, a researcher at Caltech and a colleague of Meselson's and Stahl's, conducted an experiment that supported the Watson-Crick model. When conversing with Meselson and Stahl, Holmes writes that Meselson wondered if the way he and Stahl wrote their article caused scientists to be more skeptical about how well his and Stahl's findings supported the Watson-Crick model. Holmes writes that in later interviews with Meselson, Meselson indicated less regret, but Holmes discusses the possibility of the article's focus on results at the expense of method having such an impact on the scientific community.

Holmes discusses the long-term impact of the Meselson Stahl experiment in chapter thirteen, "Images of an Experiment." Holmes pulls diagrams and excerpts about the Meselson-Stahl experiment from several textbooks, including one by Watson. As
Holmes shows, teachers often used the Meselson-Stahl experiment as a model experiment for introductory students in fields like molecular biology. Holmes also provides some scientists' input on the value of the Meselson-Stahl experiment as a teaching tool. Lastly, Holmes evaluates what scientists view as the beauty of the Meselson-Stahl experiment. According to Holmes, different scientists viewed the Meselson-Stahl as beautiful for different reasons. Holmes writes that some viewed it as beautiful for its simplicity, some for its necessity, some for its precise performance, and some for its clear results.

Holmes concludes Replication of DNA with a fourteenth chapter, "Afterward." First, Holmes makes some final statements about the importance of the Meselson-Stahl experiment and his intentions to provide the reader with a view of the world of science from the scientists' perspective. Then, Holmes describes Meselson's and Stahl's careers after the Meselson-Stahl experiment. That discussion includes Meselson's and Stahl's responses after reading a draft of Replication of DNA. Holmes asked Meselson and Stahl if reading the draft made them visualize the time that they worked at Caltech. Both scientists did remember the time, fondly.

According to John L. Heilbron, another historian of science, the significance of Replication of DNA lies not just in the material itself, but also the way in which Holmes wrote the book. In an article published after Holmes' death, Heilbron notes Holmes's approach to addressing the discrepancies between Meselson's memory and his research logs. Heilbron praises Holmes for not discrediting Meselson's memory. As Heilbron describes, like Holmes' other books, Replication of DNA places emphasis not just on scientific achievement, but also on the human element of that achievement.

Sources


In 2001, Yale University Press published Frederic Lawrence Holmes' book, Meselson, Stahl, and the Replication of DNA: A History of "The Most Beautiful Experiment in Biology" (Replication of DNA), which chronicles the 1950s debate about how DNA replicates. That experiment verified that DNA replicates semi-conservatively as originally proposed by Watson and Crick. Rather than focusing solely on experiments and findings, Holmes's book presents the investigative processes of scientists studying DNA replication. Based on personal accounts, letter correspondence, and preserved research documents, Replication of DNA serves as a detailed account of the initial issues surrounding DNA replication and the Meselson-Stahl experiment from a scientist's perspective.

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