"On the Replication of Desoxyribonucleic Acid (DNA)" (1954), by Max Delbrück

By: Hernandez, Victoria

In 1954 Max Delbrück published "On the Replication of Desoxyribonucleic Acid (DNA)" to question the semi-conservative DNA replication mechanism proposed by James Watson and Francis Crick. In his article published in the Proceedings of the National Academy of Sciences, Delbrück offers an alternative DNA replication mechanism, later called dispersive replication. Unlike other articles before it, "On the Replication" presents ways to experimentally test different DNA replication theories. The article sparked a debate in the 1950s over how DNA replicated, which culminated in 1957 and 1958 with the Meselson-Stahl experiment supporting semi-conservative DNA replication as suggested by Watson and Crick. "On the Replication" played a major role in the study of DNA in the 1950s, a period of time during which scientists gained a better understanding of DNA as a whole and its role in genetic inheritance.

"On the Replication" was Delbrück's response to two 1953 articles by Watson and Crick concerning DNA. Prior to the Watson-Crick publications, scientists had determined that genes are the biological factors that control heritable traits, which are comprised of DNA. However, the physical structure of DNA remained unknown. In addition, scientists did not know how the properties of DNA translated into the passing of genetic information from one cell to another. Watson and Crick addressed those questions in their article.

In their first 1953 article, Watson and Crick described their proposed structure of DNA. They described DNA as a double helix that contains two long, helical molecular strands. The DNA strands consist of a backbone with individual molecular units called bases attached to the backbone. Like the rungs of a ladder, in Watson-Crick DNA the DNA bases point inward so that the base of one strand joins with the base of the other, thereby providing the connecting points between the two DNA strands. Each DNA base has a specific partner meaning that each base only pairs with one other type of base. Therefore, according to Watson and Crick, by knowing the identity of the bases on one DNA strand one could determine the bases of the other strand. Joined at the bases, the DNA strands coil around each other along a vertical axis like two pieces of rope. The strands also have a beginning and an end and each run in opposite directions, so that the beginning of one DNA strand lines up with the end of the other. As of 2017, Watson and Crick's DNA structure remains the accepted structure for DNA.

In "On the Replication," Delbrück did not contest the structure of DNA that Watson and Crick had proposed, but instead he questioned the replication mechanism Watson and Crick proposed in a second article. In their second article, Watson and Crick proposed what later became known as semi-conservative DNA replication. According to Watson and Crick, because each strand of DNA contained bases that corresponded to the other strand, the strands themselves could serve as individual templates for self-replication. Watson and Crick claimed that during replication, the two strands of DNA untwisted completely and separated, each strand serving as a parent template on which new, daughter DNA strands are constructed. In their article, Watson and Crick acknowledged the issue of the strands getting tangled when uncoiled, but they dismissed the problem as something that could be overcome.

Delbrück, a researcher at the California Institute of Technology in Pasadena, California, addressed the problem of DNA strands tangling during replication with his 1954 article, "On the Replication of Desoxyribonucleic Acid (DNA)." Delbrück was a scientist educated in physics. However, when he published his article in 1954, Delbrück studied biology in search of fundamental laws that governed gene replication within basic organisms. Following the publication of Watson and Crick's articles in 1953, Delbrück wrote to Watson about how he thought the untwisting of DNA strands posed a problem for replication. He hypothesized different alternate replication mechanisms before settling on the one he wrote about in 1954 called dispersive replication.

In "On the Replication," Delbrück details his dispersive replication model and experimental designs to test that model, along with the logic and reasoning behind both. The six-page article begins with a description of the Watson-Crick model of DNA and DNA replication. Delbrück subsequently calls the model into question and proposes multiple alternative theories before settling on his favored mechanism, dispersive replication. Using diagrams and illustrations as aids, Delbrück details his model and concludes how different aspects of his mechanism could yield experimental results distinguishing the model from others. "On the Replication" ends with a brief summary and list of references.

Delbrück opens his article with a description of the Watson-Crick model of DNA and the replication mechanism that Watson and Crick suggested. In summarizing Watson-Crick DNA, Delbrück highlights how DNA bases function like a genetic code for heritable traits and how those bases are added sequentially during DNA replication. Delbrück then states that his main issue with Watson and Crick's replication mechanism is that their mechanism requires DNA strands to separate.

Delbrück describes three ways DNA strands could separate before replication. In the first way, one of the DNA strands is pulled
up while the other is pulled down, meaning that the two strands slide past each other and apart. The DNA strands are pulled apart from end to end so that the strands slide past each other vertically. In the second way, the DNA strands untwist as suggested by Watson and Crick. Delbrück writes that he rejects both of those hypotheses for how DNA strands separate because the mechanisms are inelegant and therefore inefficient.

Instead, Delbrück discusses in more detail a third way by which DNA strands could separate. According to Delbrück, DNA strands could also separate through a complex interaction of certain breaks and reunions at each interlock of the coil formed by the DNA strands. One strand could break along its backbone before each twist of the double helix, where the strands would normally get caught. The break in one strand provides a gap for the other strand to pass through, thereby avoiding tangling. The gap would then be resealed. Or, both strands break along their backbones at each twist. The segments below the breaks would then cross over each other in such a way that the twist is unwound. Lastly, each strand would join with the part of the opposing strand above the break, leaving the strands uncoiled. Delbrück argues that both of those processes are unfavorable. If only one strand breaks, the symmetry of DNA that is essential to the molecule's stability would be disrupted. If both strands broke at the same point and crossed over, they would join opposing strands in the wrong direction, because the strands run in opposite directions to begin with. Therefore, Delbrück concludes that DNA strands cannot separate prior to replication. Instead, Delbrück suggests that the separation of DNA strands and DNA replication occur simultaneously through a method he describes in the next part of his article.

In the next portion of the article, Delbrück provides a description of his replication mechanism, later called dispersive replication, in which DNA strands replicate and separate at the same time. The mechanism Delbrück proposes is a modification of the breaks and reunions method he suggests earlier in his article. Delbrück considers a case in which replication begins while the two DNA strands are still twisted together. Between each interlock of the DNA double helix, the DNA strands can pull apart slightly without fully separating, forming a bubble. Though not mentioned by Delbrück, the same can occur between two wound pieces of rope. In the gap formed between the DNA strands, Delbrück states that the replication of daughter strands can begin at each parent DNA strand. Delbrück describes that the replication continues until the assembling daughter strands meet an interlock of the parent helix. At that point, the parent strands each break along their backbones. The parent strands cross over each other, but instead of rejoining with the opposing parent strands, they rejoin with the opposing daughter strands. Each daughter strand is a replica of the opposing parent strand, so those strands travel in the same direction. Therefore, Delbrück states, when the parent strands attach to the opposite daughter strands, the parent strands attach in the right direction. The successful rejoining of DNA strands in the method that Delbrück describes can only occur if the daughter DNA strands started replicating first. The process continues throughout the entire DNA molecule, with each break occurring at each twist of the two parent DNA strands.

Following the description of his suggested alternative replication mechanism, Delbrück discusses why his mechanism is energetically favorable. Though not explicitly stated by Delbrück, chemicals are more likely to undergo a chemical change if less energy is required to achieve that change. When DNA strands separate and replicate, they undergo a chemical change that requires energy. In his article, Delbrück argues that his DNA replication mechanism requires the least amount of energy, so his mechanism is most likely to occur. Delbrück postulates that breaking and rejoicing DNA strands results in a net zero energy consumption. He also argues that no work needs to be done to correctly coil the daughter DNA strands, because those strands are automatically coiled as they are produced. Delbrück continues his discussion by stating that at any given time during replication, only one small part of the entire DNA molecule is disrupted. The rest of the molecule retains its stable, helical configuration. In contrast, if both strand of DNA were separated before replication as Watson and Crick suggested, the entire molecule would be unstable. According to Delbrück, the benefits of minimal disruption in the DNA molecule are twofold. First, the total energy use during the process is minimized. Second, only a small part of the DNA molecule needs to be uncoiled, allowing the process to occur in the tight constraints of a cell [nucleus].

The final section of "On the Replication" consists of a discussion of possible experimental results that would indicate that Delbrück's replication mechanism occurs in DNA. When Delbrück published the article, there was no experimental evidence about how DNA replicated. To craft an experimental method that would work, Delbrück first establishes that because of how parental DNA strands cross over and join with daughter DNA strands during his suggested replication mechanism, the final daughter DNA molecules would consist of alternating parental and daughter segments, thereby distinguishing the mechanism from other DNA replication mechanisms. Delbrück hypothesizes that in his mechanism if the parent DNA double helix could be labeled in some way and differentiated from newly replicated DNA, the amount of labeled and unlabeled DNA would remain equal in each new DNA double helix over many replications. Delbrück notes that other scientists had tried to label DNA by incorporating radioactive phosphorus into DNA, but were unsuccessful. Delbrück concludes his article with a brief summary.

Delbrück's dispersive replication, presented in "On the Replication," provided a plausible counterexample to the semi-conservative model of replication. While many accepted the Watson-Crick replication mechanism initially, Delbrück's article showed that questions regarding DNA replication were far from answered. In a book by historian of science Frederic Lawrence Holmes about the study of DNA replication in the 1950s, Meselson, Stahl, and the Replication of DNA: A History of "The Most Beautiful Experiment" in Biology," Holmes credits Delbrück with being the first to formally outline the issues surrounding DNA replication. Like Watson and Crick's semi-conservative model, Delbrück's dispersive replication model served only as theoretical speculation. However, as Holmes emphasizes, Delbrück provided a way to find concrete, experimental evidence supporting one model or the other.
Through his publication of "On the Replication" and afterwards, Delbrück participated in the DNA replication debate during the years leading up to the Meselson-Stahl experiment. After Delbrück suggested his alternative model, other scientists provided their own theories for how DNA replicated that challenged the semi-conservative model. Some of those scientists even communicated with Delbrück directly regarding their ideas. Watson also communicated with Delbrück privately about DNA replication after the article's publication. According to Holmes, the large response to Delbrück's article prompted Watson to question his own model of DNA and suggest counter theories to his own replication mechanism.

Between 1957 and 1958, Meselson and Stahl applied the DNA labeling method suggested by Delbrück in "On the Replication" to their own experiment. Meselson and Stahl labeled parent DNA strands and then traced the distribution of parental and daughter DNA over many replication cycles. They found that DNA replicated semi-conservatively as suggested by Watson and Crick.

Scientists used the understanding of how DNA replicates to explain how heritable traits are carried and passed down from generation to generation. In "On the Replication of Desoxyribonucleic Acid (DNA)," Delbrück initiated a discussion aimed at explaining the intricacies of DNA replication and experimentally supporting a particular theory about how DNA stores and carries genetic information. Through that debate, scientists learned how DNA replicates to preserve and pass along the information contained within it.

Sources


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