Categorization of Conservative, Semi-Conservative, and Dispersive DNA Replication Theories (1953–1956) [1]

By: Hernandez, Victoria Keywords: DNA Replication [2] Semi-conservative replication [3] Conservative replication [4] Dispersive replication [5]

In 1956, Gunther Stent, a scientist at the University of California Berkeley in Berkeley, California, coined the terms conservative, semi-conservative, and dispersive to categorize the prevailing theories about how DNA replicated. Stent presented a paper with Max Delbrück titled "On the Mechanism of DNA Replication" at the McCollum-Pratt Symposium at Johns Hopkins University [6] in Baltimore, Maryland. In response to James Watson [7] and Francis Crick´s proposed structure of DNA in 1953, scientists debated how DNA replicated. Throughout the debate, scientists hypothesized different theories about how DNA replicated, but none of the theories had sound experimental data. Stent introduced DNA replication classes that, if present in DNA, would yield distinct experimental results. Conservative, semi-conservative, and dispersive DNA replication categories shaped scientists' research into how DNA replicated, which led to the conclusion that DNA replicated semi-conservatively.

In 1953, Watson and Crick, at the University of Cambridge in Cambridge, England, proposed a structure of DNA and a possible mode of replication. They modeled DNA as a molecule consisting of two helical strands wound around a central axis in a double helix. In Watson and Crick´s DNA model, the strands consisted of a backbone facing outside the double helix, and individual units called bases that faced horizontally inward. The DNA strands connected to each other through hydrogen bonds between the bases of each strand. The bases complemented each other, meaning that each DNA base could only bind to one other kind of base, thereby making each DNA strand a template for the opposing strand in the double helix. Based on their structure of DNA, Watson and Crick proposed a way for DNA to replicate itself during cell division. Many scientists accepted Watson and Crick´s replication theory and some did not.

Max Delbrück, a researcher at the California Institute of Technology [8] in Pasadena, California, did not accept the Watson-Crick DNA replication theory. In 1954, Delbrück published a paper contesting the Watson-Crick replication theory. Delbrück´s paper started a debate about DNA replication. In his paper, Delbrück called for scientists to determine experimentally how DNA replicated. He suggested that scientists label DNA with a chemical tracker, which enabled them to observe the behavior of DNA throughout replication. After Delbrück´s publication, other scientists devised their own theories for how DNA replicated and attempted to refine the experimental methods they used to determine how DNA replicated.

Two years after Delbrück published his paper, Stent defined three broad classes of DNA replication, conservative, semi-conservative, and dispersive, while presenting "On the Mechanism of DNA Replication," which he co-wrote with Delbrück. Stent studied the experimental methods Delbrück discussed in his 1954 paper and applied those methods to the DNA of bacteriophages, which are viruses that infect bacteria. Stent categorized existing theories about DNA replication to distinguish them based on how the original, or parental, DNA strands distributed throughout newly created, or daughter, DNA double helices after successive replication cycles. Using Stent´s classes and a chemical label as Delbrück suggested, scientists could narrow down the proposed replication theories to one of the three classes.

For DNA replication theories that fell into the conservative category, the daughter double helices contained no parts of the parental DNA double helix after replication. Each replication cycle generated one daughter double helix that contained completely new material. In a chemical label experiment, if a scientist labeled the parental DNA, the daughter double helix would contain no label because it would contain no parental DNA.

According to historian of science, Frederic Lawrence Holmes, Stent proposed his own theory for how DNA replicated, which fell into the conservative category. In Stent´s DNA replication theory, a molecule other than DNA served as an intermediary between parental DNA and daughter DNA. Stent suggested that the intermediary molecule was ribonucleic acid or RNA, which could serve as a separate template for DNA replication. At the time, scientists knew of RNA´s existence, but they did not entirely know how it functioned. Scientists did know that RNA contained bases that complemented DNA bases. In Stent´s view, pairing the complementary bases in RNA with DNA bases enabled the transfer of DNA´s genetic code to RNA. The RNA instead of the parental DNA was the template for the daughter DNA strands. Therefore, the daughter DNA double helices contained no parental DNA. In other words, Stent´s mechanism conserved the parental DNA within the parental double helix. However, according to Holmes, Stent´s experiments were inconclusive.

Other researchers' proposed DNA replication theories of the 1950s fit into the conservative class, in addition to Stent´s theory. David Bloch at Columbia University [9] in New York City, New York, suggested a conservative DNA replication theory that

involved manipulation of the DNA bases to avoid unwinding the two strands. First, the bonds connecting the complementary DNA bases of opposing strands break. Next, the inward facing bases rotated in a way so that they faced outward. New DNA strands formed from each strand using the outward facing bases as separate templates. Then, the new daughter strands separated from the parent strands and joined in a complementary fashion to form an entirely new daughter double helix. The parental DNA conserved in the original DNA double helix. In his 1955 paper describing his replication mechanism, Bloch admitted that he had no current experimental evidence to support his theory.

Stent´s second category of DNA replication theories was semi-conservative replication. In contrast to conservative replication, where both strands of the daughter double helices contained new material, if DNA replicated semi-conservatively, each daughter double helix contained one parent strand and one new strand. Because parental DNA strands became part of the daughter double helices, each replication cycle yielded two daughter DNA double helices. That differed from the conservative class, in which each cycle only produced one new DNA double helix. Experimentally, if a scientist labeled parental DNA with a chemical label, that label would be present in the daughter DNA. After the first replication cycle, half of the DNA would contain the label because each of the two daughter double helices would contain one parent strand. After the second replication cycle, the labeled DNA would only make up a quarter of the new daughter DNA.

In addition to proposing their model of DNA, Watson and Crick suggested a replication mechanism that fit their model. Watson and Crick´s proposed DNA replication theory fit into the semi-conservative class. In their theory, the bonds between the bases of each DNA strand broke so that the coiled parental DNA strands could unwind and separate. Then, daughter DNA formed along the parent strands with the daughter bases complementing the parent bases. Unlike Bloch's replication theory, where the daughter strands detached from the parent strands, in the Watson-Crick theory, the daughter strands remained attached to the parent strands. Therefore, in the Watson-Crick theory, each daughter double helix contained one new strand and one parental strand, and one replication cycle created two daughter double helices.

John Platt, from the University of Chicago [10] in Chicago, Illinois, proposed another method of semi-conservative DNA replication. He suggested a replication mechanism that minimized the energy costs of DNA strands unwinding when replicating. Platt hypothesized that the parental DNA strands pulled apart from some location in the middle of the parent double helix, breaking the bonds that connected the two strands within that section. Because the strands unwound from the middle of the double helix rather than at an end, bases of each strand faced other bases within the same strand. Platt argued that bases on one part of a DNA strand could complement bases along another part of the same strand. Therefore, as the strands unwound, complementary bases within the same DNA strand caused each strand to bond with itself. During the unwinding process, each DNA strand formed a hairpin shape due to that bonding. Because of the geometry of DNA, the hairpin-shaped strands also twisted into a helix, transferring the original twist from the double helix to two separate twists within each separated DNA strand. That process, which Platt called transfer twist, minimized the energy required to unwind the DNA strands. Once the parental DNA strands existed in almost two entirely separate helices, DNA replication began at the ends of each individual DNA strand and proceeded in a way similar to the Watson-Crick process. Replication caused the self-pairing bases within each parent strand to break apart and form new bonds with the daughter bases. The resulting daughter DNA double helices each contained one new strand and one parental strand. Since one parental strand passed on to the daughter DNA double helices, Platt´s replication theory matched the semi-conservative distinction.

Stent´s last category of DNA replication theories was dispersive replication. According to Stent, dispersive replication mechanisms produced daughter DNA double helices where each strand of the double helix contained some parental DNA and some new material. That differed from semi-conservative replication because when DNA replicated semi-conservatively, the parental DNA localized in one strand, not dispersed throughout both strands of the daughter double helix as in dispersive replication. In an experiment, the first replication cycle would yield two new double helices with labeled parental DNA in each of the four strands. After multiple replications, the original parental DNA from the first replication would continue to disperse throughout all of the daughter double helices.

When Delbrück challenged the Watson-Crick replication mechanism in 1954, he suggested a theory of DNA replication that fit into Stent´s dispersive class. In Delbrück´s replication theory, DNA replication began with the strands wound together. Between each turn of the double helix, the bonds connecting the two strands broke apart. That allowed replication to start in between each twist of the double helix in a small gap between the two strands. Then, before each twist of the double helix, each parental strand broke at an identical location along its backbone. Above the break, each parental DNA strand paired with a daughter strand. Below the break, replication had not yet occurred, so the parental strands were unpaired. The bottom segments of each parental strand crossed through the break of the opposing parental strand to unwind the twist. Once the bottom segments crossed over, they each bonded with the daughter strand that was already paired with the opposite parent strand. The bonding occurred without complementary base paring. Instead, the two separate segments, the daughter segment and the unpaired parental segment formed one continuous strand. Those two segments joined because they were identical complements of the same template strand. The breaking and rejoining occurred at each twist of the parental double helix, so the new DNA strands had alternating parental and daughter material. Therefore, the parental DNA dispersed throughout the new DNA strands.

Stent´s conservative, semi-conservative, and dispersive replication classes shaped research into DNA replication following his coining of the terms. By defining three classes of DNA replication theories and distinguishing them based on experimental results, Stent emphasized the need for experimental verification about how DNA replicated. At the time, none of the theories regarding DNA replication had any conclusive experimental evidence supporting them. Stent proposed that improving

experimental tests for how parental DNA distributed into daughter DNA could help narrow down the possible replication mechanisms into one class. From that general category, scientists could better determine the exact mechanism.

In 1957, experimental improvements into distinguishing between conservative, semi-conservative, and dispersive DNA replication came when Matthew Meselson and Franklin Stahl, two postdoctoral fellows at Caltech, experimentally determined that DNA replicated semi-conservatively. What became the Meselson-Stahl experiment, the two researchers used a chemical label to track DNA over many replication cycles. The resulting distributions matched Stent's description of semi-conservative replication. Later, scientists confirmed that DNA replicated as originally proposed by Watson and Crick.

Scientists and educators frequently refer to the conservative, semi-conservative, and dispersive DNA replication classes when describing DNA replication or the Meselson-Stahl experiment. In his introductory genetics textbook, *Molecular Biology of the Gene* [11], first published in 1965, Watson referred to conservative and semi-conservative DNA replication when describing the Meselson-Stahl experiment, specifically how that experiment showed that DNA replicated semi-conservatively. Introductory biology textbooks and journal articles published after 2000 also use the replication classes when explaining the design of the Meselson-Stahl experiment. Educators often teach dispersive and conservative DNA replication alongside semi-conservative replication, even though only semi-conservative DNA replication occurs in nature. While the semi-conservative DNA replication class referred to a broader set of DNA replication theories when Stent defined the class in 1956, following the Meselson-Stahl experiment, scientists and educators use the term semi-conservative synonymously with DNA replication as proposed by Watson and Crick.

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