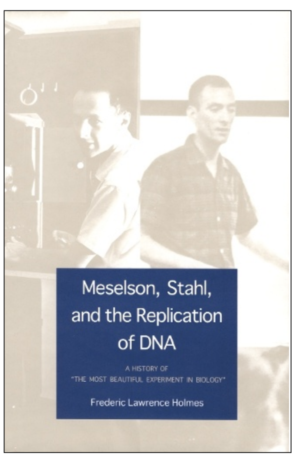
Meselson, Stahl and the Replication of DNA: A History of "The Most Beautiful Experiment in Biology"

by Frederic Lawrence Holmes
Yale University Press, $40.00, 503 pp, 2001

REVIEWED BY BRUCE STILLMAN
Cold Spring Harbor Laboratory
Cold Spring Harbor, New York, USA

Great experiments either prove a previous notion, or they reveal unexpected results that lead to new ideas. In science, ideas are propagated and the very best of them survive for many years, if not forever. Experiments are, by their very nature, often transitory and useful but for a moment in time. However, at least one notable experiment is an exception: the famous Meselson and Stahl experiment. In a recent labor of love, Frederic Lawrence Holmes delves into this experiment, telling us how it came about, how it was conceived, how it was executed and what it meant at the time. Along the way, one gets a glimpse of what it was like to do science in the earliest days of molecular biology and a sense of the social aspects of science in those heady times.



The second of the famous papers by Jim Watson and Francis Crick deals with the implications of the double-helix structure for inheritance and states that "each chain then acts as a template for the formation on to itself of a new companion chain so that eventually we shall have two pairs of chains, where we only had one before". Therein, they proposed that the DNA unwound and each strand was a template for the synthesis of a complementary strand, begetting two identical helices. They suggested that DNA might replicate in a semi-conservative manner, rather than the alternative conservative mode whereby the parental double helix remained intact and the new double helix was identical to the parent, but composed of entirely new strands. The Meselson and Stahl experiment demonstrated that Watson and Crick were correct in their assumption.

It seems difficult these days to comprehend that there was ever any doubt about how DNA must replicate. But masterfully, and in great detail, Holmes takes us back to the discourse that emerged immediately after the double-helix revelation. Many were concerned about what the great Max Delbrück thought of the double helix, and although he enthusiastically spread the word about its structure, true to form, Max had a problem: the "untwiddling problem". How could the two strands that were intertwined so many times separate during replication? He was not only concerned about the problem, as were Watson and Crick, but he proposed a complicated (and incorrect) solution in a *Proceedings of the National Academy of Sciences* paper in the Spring of 1954.

Holmes' well-written book describes every detail from thenceforth. The chance meeting of Matt Meselson and Frank Stahl at Woods Hole, the seminar by Monod that induced Meselson to think about density transfer, the trials of experimentation and of course the "beautiful experiment" itself. Although dense, the story is worth reading to understand what science was like in the 1950s and how a great experiment came about. It also describes the environment at Caltech during that era, scientifically exciting, but socially bleak. I assume the social environment in Pasadena has improved, but clearly the science there remains as strong as it was. Students who do science, or those who study the process will learn much from this book on how great science can be accomplished.

What struck me while reading this treatise was the remarkably open exchange of ideas between the early phage investigators, via letters and discussions at meetings. Scientists traveled (and reveled) more than I would have thought, a common thread that has emerged in other books I have read about the early phage days. For example, Holmes reports that Meselson and Stahl wrote many times to Jim Watson and others about the design and progress of their experiments. Obviously Watson had a more than passing interest in the matter, but more interestingly, Meselson and Stahl wrote to and visited Gunther Stent at Berkeley to discuss their progress. They did this even though Stent was working on the replication problem and favored the Delbrück proposal that DNA replication was not semi-conservative. We should learn from history, because unfortunately, in modern molecular biology where scientists are not as technique-limited as they once were, the free exchange of ideas is in danger of being lost.

The measure of a great technique is what it reveals and whether it lasts. The Meselson and Stahl experiment is still in wide use today. It has been used to demonstrate the distributive nature of histone deposition during chromosome replication and most recently to study the mechanism and timing of replication of the entire genome of the yeast *Saccharomyces cerevisiae*. Very few experimental methods have survived as long as the density-transfer idea. Thus, I expect that Holmes' book will be read for many years to come, and justifiably so.

REVIEWED BY SYDNEY BRENNER
Salk Institute for Biological Studies
La Jolla, California, USA

In these days of high throughput science, when advances in technology have literally given us the power to make atom-by-atom descriptions of all living matter, it is refreshing to look back at an earlier time, when advances in science required both a good idea and the means to show it was true. We were like Houdinis, strapped in chairs with our hands tied behind our backs trying to escape from locked rooms. This book is the history of the Meselson–Stahl experiment—the most beautiful experiment in biology—and reconstructs both the background and the event itself in a most meticulous and admirable way. Although we learn about the revolution in biology consequent upon the discovery of the double helix, it is not history in the large but rather history on the minute scale of what actually happened in the creation and execution of the experiment. The author has had access both to the notebooks and the memories of the scientists as well as to others and he has marshaled all of this detail into a narrative that is interesting and informative.

When the double helical structure of DNA was proposed, the intertwining of the strands created an objection in the minds of some who became concerned that the strands would have to be unwound in order for them to be replicated. Max Delbruck, in particular, was most troubled by it. It was fortunate that, at the time, people did not know that there were DNA molecules that were closed circles, because they would have declared the replication model proposed by Watson and Crick impossible. Somewhere the book says that there was a small band of enthusiastic supporters who were not troubled by this difficulty. I was one of them and took the view that if it were a problem, biological systems would have found a way to solve it. Indeed, I think it was Leslie Orgel who said that nature would have invented an enzyme to do it, a most perceptive insight.

The consequences of the replication model were clear: after one replication step two molecules would be present, each with one old and one new strand. How could one prove this? I met Matt Meselson outside Blackford Hall in Cold Spring Harbor in September 1954 when he had already conceived of the idea of doing the experiment with heavy isotopes using some sort of density centrifugation to separate the molecules. Frank Stahl knew how to work with phages and the partnership was formed. However, Meselson had to complete his PhD thesis research in crystallography, and while making the transition from physical chemistry to biology, he kept detailed notes about what he was reading in a workbook. The evolution of his thinking can be followed from these books.

After spending time trying to do the transfer experiment with 5-bromouracil-labeled bacteriophage T2, density-gradient ultracentrifugation became possible and they switched to using bacteria and ^{15}N labeling. They were able to show that the difference in density between light ^{14}N- and heavy ^{15}N-labeled DNA was sufficient to allow a molecule of intermediate density to be resolved, whereupon Meselson decided to do a double-transfer experiment from heavy to light and light to heavy medium against the advice of Stahl who had to go to an interview in Missouri. Meselson also added several controls and labeled the tubes from this large series of experiments with a complicated code before proceeding to analyze them in the ultracentrifuge. His memory was that the experiment had worked, but an examination of the original films showed that his recollection of the result was wrong. None of the films showed the expected three bands that Meselson thought he saw when he rushed over to announce the result at a party being held at his house. Of course, later experiments gave the expected result.

It could be said that if historians have the benefit of hindsight, scientists have the advantage of foresight. Meselson had sketched the expected result before doing the experiments and I think he superposed in his mind the individual results of his experiments to generate an answer compatible with it. All experimentalists know you have to do an experiment four times. The first one is a complete mess and shows only a hint that it might have worked. The second one is better but still messy. Then you do it the third time for the book. This is when you forget to add a reagent, or mix up the tubes or the centrifuge leaks. That is why there is always a fourth time.

I urge every young scientist to read this book. In 1957, when the experiment was performed, Meselson was 27 and barely with a PhD in chemistry. Frank Stahl was 28 and a postdoctoral fellow at the California Institute of Technology. Both were doing an experiment that had nothing to do with their official programs of research. They simply went ahead and did it. They filled out no forms, made no applications, had no reviews. They only had the judgments of their real scientific peers.