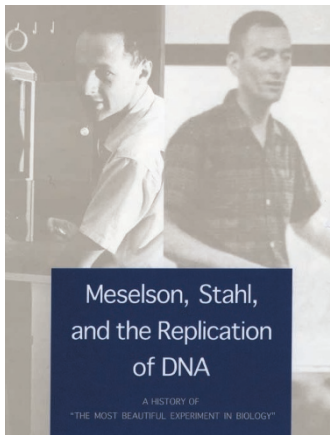
Heavy-strand Leitmotiv



Meselson, Stahl and the Replication of DNA
by Frederic Lawrence Holmes
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Which books convey the excitement of the early years of molecular biology? Horace Freeland Judson's *The Eighth Day of Creation* published over twenty years ago succeeds as a vivid narrative, surveying highlights up to the early 1970's. Alternatively, autobiographical accounts give a flavour of the times, with James Watson's *The Double Helix* probably being the best known. Frederick Holmes' book is more unusual in that it focuses on a single experiment, probing in detail the research that led to a classic paper. Rather than just giving a synopsis of events, this book goes into the day to day activities of Matthew Meselson and Frank Stahl over a four year period in the mid 1950s that led to the graphic demonstration that DNA replicates semi-conservatively. The result is an honest and refreshingly unretouched account, showing that nothing in science is as simple as it might seem.

Why does the Meselson–Stahl experiment deserve such special treatment? The structure of DNA has become such a cornerstone for biology, an experiment that demonstrated the basic mechanism of DNA replication might seem now just to have confirmed a strong expectation. It is difficult to think back to the uncertainties some 50 years ago, when the Watson–Crick structure was greeted in some quarters as 'an ingenious speculation'. Part of the problem lay with the double helix itself. Base complementarity solved the problem of how genetic information could be replicated, but the two strands have to be unwound in the process. Although now we understand how enzymes carry this out, it wasn't intuitively obvious at the time how an extremely long, double-helical molecule could be unzipped for replication. In fact, various complicated models involving, for instance, frequent strand breakage and rejoining were devised to get round this 'untwiddling' problem. Max Delbrück, the leader of the influential Caltech phage group, rejected unwinding of the double helix as too inelegant to be efficient but had the insight to propose an experimental test. By following how label in the parental strands of a DNA molecule is distributed following replication, the semi-conservative prediction from the Watson-Crick structure could be distinguished from more complex schemes. Meselson and Stahl provided the technical skill necessary for this demonstration in an experiment that is so elegant in design and had a result so unambiguous that John Cairns described it as "the most beautiful experiment in biology". The critical technical innovation was to use cesium chloride (CsCl) gradients in the ultracentrifuge, which allowed parental and daughter DNA strands to be distinguished by using a heavy isotope of nitrogen.

The basics of the Meselson–Stahl experiment can be found in any genetics textbook. In terms of detail, Frederick Holmes' meticulously researched account is at the other end of the spectrum. This book sets the scene by describing uncertainties in DNA replication, and the chance meeting of Meselson and Stahl at a summer school in Woods Hole, Massachusetts. The concept of the experiment had already occurred to Meselson, who thought up the idea of using dense isotopes to follow protein synthesis (finding inspiration during a Jacques Monod seminar), and later saw the method might be more useful for DNA replication. Stahl had the technical background in bacteriophage, which seemed at first the obvious choice for the experiment, and the collaboration was born. To say the rest is history though would be to obscure the fact that the final experiment might not have been done and was only arrived at by a doglegged route. Apart from getting thesis work out of the way, there were many distractions, such as attempting to understand mutagenesis and using density gradients for other experiments. Chance, as much as cold logic, influenced the final design. The choice of *Escherichia coli*, which allowed replication over successive cell cycles to be followed, was only made after initial work with phage T4 were unsuccessful (T4's DNA replication is complicated by recombination). Had they started with another phage such as λ, the experiment would have worked but not with such a beautiful result.

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This book is a rewarding if, in places, a demanding read. Holmes is a historian, but he doesn't blanch at giving finer details of phage genetics, nucleic-acid chemistry and the physics of centrifugation. As the plot reaches a climax, numerous ultracentrifuge films and even doodles on log sheets are subject to scrutiny. Even if all these details are not essential, what does come across is the intensity of the effort that is needed to get innovative experiments to work. Holmes completes the story by giving a critique of the final paper and reflects on its impact both at the time and later, as an iconic experiment.

As a commentary on how science is done, times have changed and reflecting on the current climate one reviewer remarked "I cannot imagine a graduate student or post-doc taking the risks that Meselson and Stahl took". But some of the lessons are still useful and innovative techniques in biology are as valuable now as they were half a century ago. Meselson in fact wrote to Stahl in 1959 "CsCl has an inexhaustible number of golden eggs to lay" and to make the point it proved crucial for the discovery of messenger RNA just two years later. □

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