"The most beautiful experiment in biology." That was how John Cairns described it: the 1958 experiment that showed how the genetic material, DNA, replicates. The work is still widely celebrated, sometimes in introductory biology textbooks.

This esteemed experiment by Matt Meselson and Frank Stahl (described more fully below) and others like it reflect an ideal in science, marked by an intuitive aesthetic response. The test was simple. The results were clear. The method and reasoning seemed obvious. Theory and evidence complemented each other elegantly. That seems to be how science works—or should work.

However, this view of biology, so common as to be beyond question—another sacred bovine?—can be misleading. Appearances can be deceptive. In this case, delving into the history of the now famous experiment fosters a very different image. Behind the apparent simplicity hides extraordinary—and fascinating—complexity. A glimpse of the messy world of investigation indicates how science really happens, quite apart from the tidy scientific method that one finds in standard textbooks. Ultimately, the messy story behind the most beautiful experiment in biology offers a quite different, and deeply informative, way to appreciate science.

A Beautiful Experiment

The experiment developed from a puzzle about how DNA, the genetic molecule replicates. In 1953 James Watson and Francis Crick, building on data from Rosalind Franklin and Maurice Wilkins, presented a model of DNA's molecular structure. It was two threads that coiled around each other, they claimed. Like two intertwined strands of rope. That double helix model has since been widely celebrated and inspired much art.

But how did the DNA molecule replicate? When any cell divides, each new cell receives a complete set of information. Duplicate copies of DNA are assembled. But how? The Watson-Crick model offered a partial solution. The genetic information was a sequence of units, called nucleotides that bridged the two strands. They occurred in pairs. The shapes in each pair were complementary. So, the shape of one side would determine which missing base would pair on the other. Units could self-assemble blindly. But one detail remained unclear. Did the original molecule act as a template for making two new strands that joined with each other? Or did the original split, with each half pairing with its own new strand?

While the alternatives are easy enough to envision with cardboard cut-outs or hand-held models, the challenge was to make such events on a molecular scale visible experimentally. That is just what Meselson and Stahl did. They solved the puzzle, showing in 1958 that DNA replicates "semi-conservatively," distributing the original DNA strands half and half in each cell generation.

The solution involved two experimental innovations. First, Meselson and Stahl invented a way to identify the new strands versus parent strands. Second, they developed a method to separate the different forms of DNA resulting from successive replications. The new strands were assembled using different atomic isotopes, with a modestly heavier molecular weight. Separation then occurred by spinning at high velocities in a centrifuge tube. By using a heavy salt solution, they established a density gradient as the tubes spun rapidly. Heavy molecules would sink, and light molecules, by contrast, "float." Each molecular weight would drift and at equilibrium find a distinct level in the gradient. The resulting bands of DNA material at each generation were visually definitive: “perfect Watson-Crickery,” as celebrated by one researcher.

The experiment epitomized good practice in several ways. First, it captured a central theoretical question in a single experiment. The problem of DNA replication was certainly not new. Watson and Crick’s model had puzzled researchers for several years. Imagining possible events at the molecular level is relatively easy. Manifesting them in the lab is quite another thing. Sometimes, the molecular realm is revealed piecemeal, in clues and partial glimpses. Here, one well oriented probe sufficed.

Second, Meselson and Stahl’s experimental design addressed all the alternative theoretical models of replication simultaneously. If they failed to confirm one model, they would not have to then tests the others.

Third, the experiment was marked by laboratory expertise. Material skills matter as much as thinking. The results were “clean” and unambiguous.

Finally, the team also introduced a new method of wide scope. The technique of using heavy isotopes to differentiate macromolecules, once demonstrated, could be applied to many other studies.

Meselson and Stahl’s experiment thus exhibited creative arrangement of laboratory conditions, theoretical import, clarity, and craft skills, all while pioneering an important new method. Rarely do all such elements come together in one work. When they do, scientists justly celebrate.

Typically, we associate beauty with works of art or design. Yet our aesthetic sense of unity and harmony responds whenever form and function match. Scientists thus come to regard some experimental designs as elegant. They appreciate how a set of observations may be specially configured to yield a decisive interpretation. No procedure is unnecessary, no effort wasted. Stahl himself later commented on the perceived beauty in his experiment:

> It's very rare in biology that anything comes out like that. It's all so self-contained. All so internally self-supporting. Usually, if you are lucky to get a result in biology, you then spend the next year doing all those plausible controls to rule out other explanations; but this one was just a self-contained statement.

Meselson and Stahl's experiment was beautiful because the experimental methods and theoretical results fit together so fully, yet so minimally. No wonder that the work is sometimes featured in biology textbooks, where it can exhibit scientific ideals.

A Messy History

The ultimate outcome was beautiful. But how did it emerge? How do such notable achievements in science unfold? How did Meselson and Stahl originally conceive their novel experiment? What shaped its groundbreaking conditions? Indeed, how do scientific discoveries happen? Historian Larry Holmes documented the episode by examining lab records, interviewing the scientists, and plumbing institutional details. Viewed as a creative process, the experiment proved to be far from simple. Ultimately, the account filled a 500-page book.

Matt Meselson and Frank Stahl met as graduate students in the summer of 1954 while at Woods Hole Biological Laboratory. Matt was a course assistant for James Watson himself. Frank was taking another course not available at his home institution. Stahl was drinking a gin and tonic under a tree. Watching from the main building, Watson remarked on his reputed fine lab skills. Meselson, curious, went to introduce himself. Frank had been considering a statistical problem requiring calculus. Several days later, Matt offered a solution, impressing Frank in turn.

An enduring friendship developed. Before the summer was out, Meselson had mentioned a prospective study on DNA replication and Stahl had structured it experimentally.

Where had Meselson's idea come from? Early in 1954 he had been working on problems on deuterium, a heavy isotope of hydrogen, as part of a course with Nobel-Prize winning chemist Linus Pauling. He wondered whether organisms would live in "heavy water," made with the heavy hydrogen isotope. Later that spring, a visiting lecturer, Jacques Monod, had spoken on how cells can be induced to produce new enzymes. Meselson then imagined how by growing the cells in a medium with the heavy isotope, it would be incorporated into the new proteins. One could then separate the new proteins from the old in a solution with an appropriate density. The old proteins would float to the top, while the new, slightly heavier ones sank to the bottom. The core design for the later experiment on DNA was thus first developed in an entirely different context.

A few months later, a molecular biologist, Max Delbrück, introduced Meselson to his ideas on DNA replication. He speculated that the original paired strands of DNA would remain intact, but because replication would occur in short isolated segments, the resulting old and new fragments would be interspersed, spliced into patchwork strands. Meselson saw another application of his heavy isotope scheme—the one he shared with Stahl at Woods Hole in the summer of 1954.

But the route to the last run of the experiment in February, 1958—over three years later— was hardly direct. Before long, the heavy deuterium was replaced by 5-bromouracil, very similar to the thymine unit in DNA. It would substitute directly for thymine during DNA synthesis. The weight difference would be more dramatic, and thus it would be easier to separate different DNA strands.

This, in turn, led the team to a wholly different line of investigation on using 5-bromouracil to induce mutations, which could then be studied in more detail. Soon the second question became primary. Pursuing that new trajectory, they searched for a solution with an appropriate density. Would potassium bromide work? No. Magnesium sulfate? No. Barium perchlorate? No. Cesium chloride? Perhaps. But at what concentration? More brute trial and error. Then they tried the new technique, only to discover that centrifuging the solution destroyed the homogenous density. To their dismay, they produced a density gradient instead. They had planned to separate the DNA in *discrete* layers, using solutions of uniform known density. Fortunately, the gradient was gradual enough. The key molecules would still separate and spread themselves out according to their weight. Nonetheless, they explored a possible alternative: separating the molecules in a gel medium subjected to an electric field. One method led to another, and another still. Lots of trial and error.

In August 1957, Meselson saw an advertisement for an isotope of nitrogen, nitrogen-15. They had rejected it earlier, assuming that the weight difference with DNA using nitrogen-14 would be too small to measure. However, the unexpected resolving power of the density gradient method now made it possible once again. Suddenly, 5-bromouracil was abandoned. The mutagenesis inquiry was set aside. The experimental design so celebrated by history finally emerged.

But there were other practical challenges, as well. The two researchers competed for time on the centrifuge, a huge (and costly) instrument shared by many labs. A sample run might take 20 hours or more. Then they had to find the appropriate spinning speed, finally settling on nearly 45,000 revolutions per minute, producing a force over one hundred thousand times the force of gravity. They needed to identify a chemical to break open their bacteria cells without also destroying the DNA molecules. Meanwhile, their regular work continued. Meselson had a doctoral thesis to write—on an unrelated topic. There were job interviews. And so on. If the final experiment was simple, the process was anything but.

Real science hardly resembles the cookbook labs one frequently encounters in school classrooms. Nor is it the formulaic scientific method enforced on many science-fair projects. Of course Meselson and Stahl's investigation may be edited and reconfigured in retrospect to fit a simple step-by-step logic from hypothesis to experiment, results, and conclusion. But the historical view, in real time, reveals a far less orderly or directed history. The outcome was beautiful. However, the process was messy.

A Hidden Reward

Science is filled with chance encounters, metaphoric thinking, false starts, tinkering, unsuccessful explorations, and plain hard work. As illustrated in this case, science is a creative enterprise that collects isolated moments of imagination and available resources and knits them into multiple possible trajectories. Ultimately, unlikely arrangements of methods and observations can yield something both coherent and meaningful. The final product can be simple enough and pretty enough for textbooks. But that idealized version may well disguise how it unfolded. The Meselson-Stahl experiment emerged unpredictably from a series of events, sometimes shaped by considerations unrelated to the project's ultimate aim. Yet we can appreciate the convoluted history as much as the beauty of the polished product. Great science can emerge from a complex, unpredictable process.

The messy history of Meselson and Stahl's beautiful experiment illustrates nicely the rewards of probing the commonplaces that govern our thinking about biology: our sacred bovines. Challenging assumptions can lead to unexpected discovery—and with it the reward of deeper insight. That is the sense of adventure that guides the many explorations in succeeding chapters.