The Most Beautiful Experiment

Every life starts out as a single cell containing an entire genetic blueprint, or genome, in the form of DNA. That cell divides from one into two, and then from two into four, and so on, each new cell receiving a copy of the genome.

This process—how DNA replicates itself—was a topic of debate in the mid-1950s, including at Caltech. In 1958, two Caltech researchers conducted an experiment that definitively settled the question and, in the process, revolutionized the fields of biology and genetics.

This year marks the 60th anniversary of the publication of a paper describing the effort. "The Meselson-Stahl experiment has been called the most beautiful experiment in biology for the elegant logic of its deceptively simple design," says Judith Campbell, Caltech professor of chemistry and biology.

At the time, there were three leading theories for how DNA copies itself into new cells:

1. Conservative: The parent double-helix DNA is copied in its entirety, and the new cell's DNA is entirely a copy of the old.
2. Dispersive: DNA is chopped up into pieces; these little pieces are copied and then reassembled in combination with the old pieces.
3. Semiconservative: The double-stranded DNA separate from their helix shape, and each makes a copy of itself. The new cells then contain one strand from the parent cell and one newly synthesized strand.

Many scientists, including Caltech professor and soon-to-be Nobel Laureate Max Delbrück, did not believe the semiconservative model possible, because they reasoned that a tightly bound double-stranded helix of DNA should not be able to separate into its two constituent strands.

While working one summer at the Marine Biological Laboratory in Woods Hole, Massachusetts, Caltech graduate student Matthew Meselson met fellow visiting graduate student Franklin Stahl, who—as they tell it—was sitting underneath the shade of a tree, selling gin and tonics to passersby. The next year, when Stahl was at Caltech conducting postdoctoral research, they designed an experiment to discover how DNA replicates itself.

First, the researchers grew a strain of bacteria in an environment with a type of "heavy" nitrogen, ^{15}N, that contains an extra neutron. Since nitrogen is a key part of DNA, each bacterial cell now contained heavy DNA. When placed in a centrifuge—a device that spins and separates out molecules by their density—this DNA settled near the bottom.

Then, these cells were placed in an environment with light nitrogen, ^{14}N. After one generation of cell division, the new DNA was also placed in the centrifuge. Its density showed that it was composed of half heavy nitrogen and half light, ruling out the theory of conservative DNA replication, which would predict that the new DNA would have had to be copied in its entirety, using the light nitrogen in the cell's new environment.

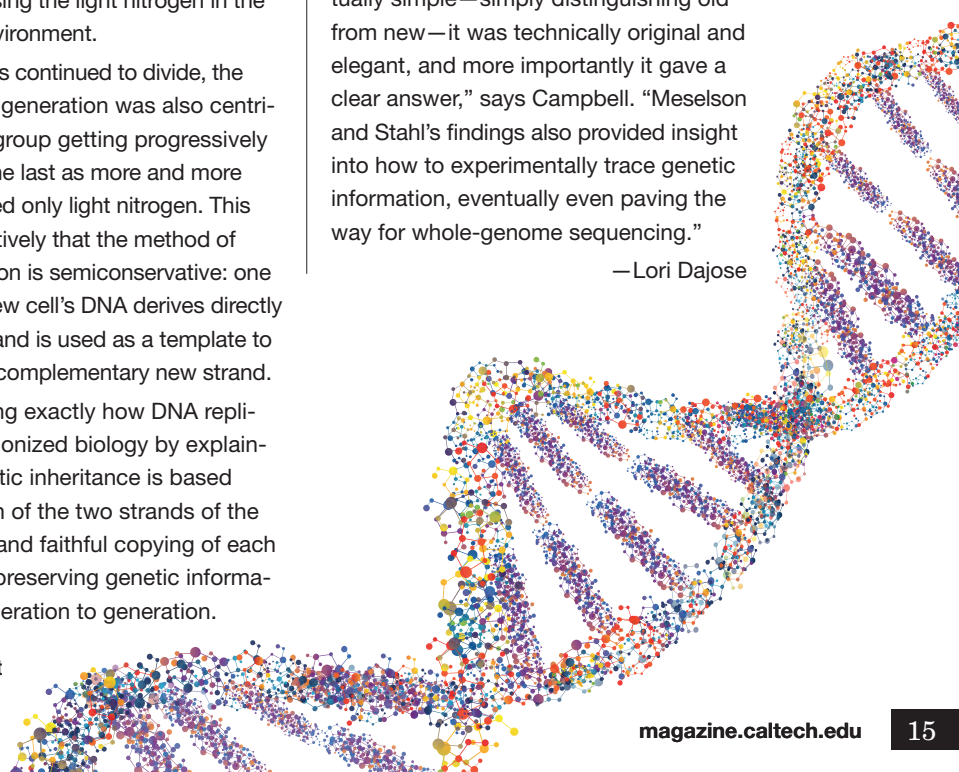
As the cells continued to divide, the DNA of each generation was also centrifuged, each group getting progressively lighter than the last as more and more cells contained only light nitrogen. This proved definitively that the method of DNA replication is semiconservative: one strand of a new cell's DNA derives directly from the old and is used as a template to synthesize a complementary new strand.

Discovering exactly how DNA replicates revolutionized biology by explaining that genetic inheritance is based on separation of the two strands of the double helix and faithful copying of each strand, thus preserving genetic information from generation to generation.

Matthew Meselson, one of the pair of Caltech researchers who, in 1958, definitively settled how DNA replicates itself.

The experiment addressed a question that constituted a century-old roadblock to understanding how the structure of DNA led to its functions—inheritance, mutation, and information storage for protein synthesis. "While it was conceptually simple—simply distinguishing old from new—it was technically original and elegant, and more importantly it gave a clear answer," says Campbell. "Meselson and Stahl's findings also provided insight into how to experimentally trace genetic information, eventually even paving the way for whole-genome sequencing."

—Lori Dajose



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