

# Max Ludwig Henning Delbrück (1906–1981)

Max Ludwig Henning Delbrück applied his knowledge of theoretical physics to biological systems such as bacterial viruses called bacteriophages, or phages, and gene replication during the twentieth century in Germany and the US. Delbrück demonstrated that bacteria undergo random genetic mutations to resist phage infections. Those findings linked bacterial genetics to the genetics of higher organisms. In the mid-twentieth century, Delbrück helped start the Phage Group and Phage Course in the US, which further organized phage research. Delbrück also contributed to the DNA replication debate that culminated in the 1958 Meselson-Stahl experiment, which demonstrated how organisms replicate their genetic information. For his work with phages, Delbrück earned part of the 1969 Nobel Prize for Physiology or Medicine. Delbrück's work helped shape and establish new fields in molecular biology and genetics to investigate the laws of inheritance and development.

Delbrück was born on 4 September 1906, as the last of seven children of Lina and Hans Delbrück, in Berlin, Germany. Delbrück grew up in Grunewald, a suburb of Berlin. In 1914, World War I began. During the war, Delbrück's family struggled with food shortages and in 1917 Delbrück's oldest brother died in combat. After the war ended in 1918, Delbrück began to study astronomy. Some nights, Delbrück woke up in the middle of the night to observe the stars with his telescope. He also read about the seventeenth-century astronomer Johannes Kepler, who studied planetary motion in late sixteenth and early seventeenth century Germany. Delbrück graduated from high school in 1924 and wrote his graduation speech on Kepler, using 300-year-old books from a nearby library as his resources.

After graduating, Delbrück studied astronomy and physics in college. In 1924, he first studied astronomy at the University of Tübingen, in Tübingen, Germany. The following semester, Delbrück attended the University of Berlin, later renamed Humboldt University of Berlin, in Berlin, Germany, because his father taught there and could not afford to pay for Delbrück's tuition elsewhere. After switching between several German universities, in 1926 Delbrück settled at the University of Göttingen, in Göttingen, Germany. Delbrück initially pursued his PhD in astronomy at Göttingen, but later switched to quantum physics, the study of the behavior of atomic and subatomic particles. In Delbrück's biography, written by Ernst Peter Fischer and Carol Lipson, the authors state that Delbrück switched fields because German scientists made significant advancements in quantum physics that made the field attractive. Furthermore, the literature on the topic was primarily in German, whereas literature about astronomy research was in English, which Delbrück could not read. In 1930, Delbrück received his PhD for his work on the quantum aspects of a lithium atom.

Around the time he completed his PhD, Delbrück began holding postdoctoral positions throughout Europe and continued to do so during the 1930s. During the summer of 1929, before Delbrück received his PhD, he started a fellowship at the University of Bristol, in Bristol, England. At Bristol, Delbrück gave lectures on quantum physics in spite of being unable to speak English. In 1931, Delbrück received a one-year fellowship from the Rockefeller Foundation, headquartered in New York City, New York, which routinely funded scientists to perform research internationally. As part of his fellowship, Delbrück worked with two Nobel laureates: Wolfgang Pauli at the University of Zürich, in Zürich, Switzerland, and Niels Bohr at the University of Copenhagen, in Copenhagen, Denmark.

Delbrück claimed that his interest in biology stemmed from Bohr and their work together in 1931. During a 1932 lecture titled "Light and Life" that Delbrück attended, Bohr attempted to extend ideas of quantum physics to other fields, including biology. Bohr spoke of a complementary phenomenon in physics, in which matter exhibits particle and wave-like properties with different laws governing

each. He proposed that as with quantum physics, complementary laws could be found in biology. Bohr stated that scientists needed to find those complementary phenomena to fully explain biology. According to Delbrück, the lecture inspired him enter the field of biology.

After completing his Rockefeller fellowship in 1932, and spending a few months at the University of Bristol, Delbrück returned to Berlin to work at the Kaiser Wilhelm Institute of Chemistry, later called the Max Planck Institute of Chemistry, where he remained from 1932 to 1937. In his position, Delbrück focused on quantum physics, but he also pursued biology. For his biology pursuits, he launched interdisciplinary research meetings that took place at his Berlin home in Grunewald. Nikolai Timoféef-Ressovsky and Karl Günter Zimmer, who both studied *Drosophila*, or fruit flies, in the 1900s, attended some meetings and later collaborated with Delbrück to publish a paper in 1935 about genetic mutation caused by radiation in *Drosophila*. That article was Delbrück's first public contribution to biology. When Delbrück and his colleagues published the paper, scientists still were not able to explain the exact structure of genes, or whether genes were proteins or nucleic acid. While some of the findings in the paper were not supported by later research, quantum physicist Erwin Schrödinger obtained the paper and talked about Delbrück's contributions to genetics in the book *What is Life?* published almost ten years later. According to Delbrück's biographers, many scientists, including DNA scientists James Watson and Gunther Stent, wanted to work with Delbrück after reading *What is Life?*. Delbrück's early contributions to genetics as mentioned by Schrödinger made Delbrück known throughout the scientific community.

In the midst of Delbrück's early work in biology, in 1937, the Nazi regime rose to power in Germany. Subsequently, Delbrück left Germany for a Rockefeller Foundation fellowship at the California Institute of Technology, or Caltech, in Pasadena, California. The Nazi regime required all university employees to participate in certain discussion groups. The members of the Nazi party did not deem Delbrück politically mature enough to hold a university position. In a later interview, Delbrück claimed that he was most likely declined a position because he was too vocal about his dislike of the Nazi party. Around the same time, the Rockefeller foundation started a program to help the scientists Hitler and the Nazi party had displaced. As part of that program, the Rockefeller Foundation funded a position for Delbrück to work with the Thomas Hunt Morgan research group to apply physics to studying the genetics of mutations of *Drosophila* at Caltech. In June 1937, Delbrück received his exit visa and left Germany.

Delbrück only briefly studied *Drosophila* with the Morgan group before pursuing research on phages in the US. In late 1937, Delbrück met Emory Ellis, a cancer researcher who also studied bacteriophages at the Kerckhoff Laboratories of Biology at Caltech. Delbrück took a tour of Ellis's lab, where Delbrück saw phage-infected *Escherichia coli* bacteria. While scientists later utilized *E. coli* quite frequently, few scientists knew much about the bacteria. In his interview with Harding, Delbrück commented on the holes, called plaques, present in petri dishes where bacteria grew. On a plate of bacterial cells, plaques appeared when bacteria died due to phage infections. The presence of more phages lead to more plaque-causing infections, so Ellis used the plaques to measure phage growth. In 1938, Delbrück joined Ellis to work with phages. The two researchers found a quantitative way to measure phage replication and published their findings in 1939. Delbrück and Ellis's researched enabled other phage scientists to more accurately measure phage replication and study phage infections. The researcher's collaboration ended when Ellis returned to his cancer research in 1939.

In 1939, Delbrück renewed his Rockefeller Foundation fellowship for a position as a physics instructor at Vanderbilt University in Nashville, Tennessee. According to Delbrück, the start of World War II dissuaded him from returning to Germany. After receiving the new position, in 1940 Delbrück met Mary Adaline Bruce in Pasadena and phage researcher Salvador Luria at a conference for the American Association for the Advancement of Sciences in Philadelphia, Pennsylvania. The following year, Delbrück married Bruce and began his major collaboration with Luria on phage research.

From 1941 to 1943, Delbrück and Luria studied phages together. During the summers, they worked in person at the Cold Spring Harbor Laboratory in Cold Spring Harbor, New York. Throughout the rest of the year, they worked separately, with Luria conducting the experiments and Delbrück analyzing the data. Delbrück and Luria's research centered on bacterial resistance to phages. Bacteria resistant to a particular phage can continue to grow and divide even in the presence of that phage.

At the time, scientists proposed that genetic mutation caused the resistance, but they did not know what caused the mutation. Researchers had two hypotheses for the cause. They hypothesized that either the mutations were spontaneous, as in other more complex organisms, or that exposure to the phage induced the mutations. Delbrück and Luria aimed to determine how the mutations arose.

The researchers worked with a strain of *E. coli* that they knew could be infected by phages. In several different petri dishes, they exposed *E. coli* to phages. The *E. coli* divided rapidly. As the bacteria continued to replicate, different mutations arose that made the bacteria resistant to the viral infections. Therefore, Delbrück and Luria knew that the surviving bacteria had undergone some mutation and that the dead bacteria did not mutate. Delbrück and Luria exposed each petri dish to the same amount of phage. If the mutations had been caused by exposure to the phage, all the petri dishes would have exhibited the same number of surviving, mutated bacteria. If the mutations were random, each petri dish would contain a different number of surviving bacteria.

When analyzing the *E. coli* after phage exposure, Delbrück and Luria noted that the number of surviving bacterial colonies, or clusters, varied between petri dishes. Some petri dishes had no colonies, meaning that the phages had killed all the bacteria and that no bacteria mutated. Other petri dishes had many colonies, indicating that many bacteria mutated to become resistant to phage infection. The number of colonies fluctuated for the same sample, leading Delbrück and Luria to conclude that the resistance-causing mutations were spontaneous and random. Delbrück and Luria's experiment, called the Fluctuation Test, provided evidence that genes in bacteria underwent random mutations and therefore behaved like genes in higher organisms. Scientists later utilized bacterial genetics to study gene expression and genetic engineering.

After performing the Fluctuation Test with Luria, Delbrück continued to spend most of his summers at the Cold Spring Harbor Laboratory. Initially, Delbrück spent those summers alone studying phages, but later he and Luria made Cold Spring Harbor a central location for scientists studying phages. The scientists who met in Cold Spring Harbor later became members of the Phage Group. The group unified phage research by encouraging cooperation and collaboration among phage researchers. For example, in 1944 Delbrück negotiated with other phage scientists to standardize the field by agreeing to only study the same seven phage strains. The following year, Delbrück introduced annual courses at the Cold Spring Harbor Laboratory on phage genetics. The courses along with unofficial discussions among scientists studying phages evolved into formal phage research meetings held in Nashville in 1947, and then from 1950 onward in Cold Spring Harbor. Annual phage meetings continued throughout the rest of Delbrück's life.

In December 1946, Delbrück returned to Caltech to serve as chair of the biology division. According to his biographers Fischer and Lipson, Delbrück's early phage work with Luria did not help him with his primary goal to understand phage replication. Rather than continue to study mutations in bacteria, Delbrück moved his focus back to gene replication, particularly in phages.

During the 1950s, Delbrück became involved in a debate over the mechanics of DNA replication. In 1953, James Watson and Francis Crick published their double helix model of DNA, in which the two strands of DNA wound around each other like a rope. At the time, scientists had just begun to accept DNA as genetic material. Along with the model, Watson and Crick suggested a self-replication mechanism of DNA that explained the passing of genetic information from generation to generation or inheritance. The model, later called semi-conservative replication, involved the two helical strands of DNA unwinding and splitting apart to serve as individual templates for new DNA strands. While some scientists immediately accepted the mechanism, Delbrück questioned the model.

Delbrück contested how DNA strands separated in the semi-conservative replication mechanism. He questioned whether or not the two DNA strands could unwind as Watson and Crick suggested and whether or not scientists could actually experimentally test for the mechanism. In 1954, Delbrück wrote his own theory for DNA replication, later called dispersive replication, in which the DNA strands broke apart into smaller pieces to separate and self-replicate. Delbrück also suggested ways in which scientists could experimentally determine the method of DNA replication. Following the publication of Delbrück's paper, scientists debated about how DNA replicated and how they could determine what replication theory occurred in nature. Delbrück and Stent, who also studied DNA

and phages, followed up the 1954 paper with a 1956 presentation outlining the new theories and possible experiments. The DNA replication debate lasted until 1957, when Matthew Meselson and Franklin Stahl conducted the Meselson-Stahl experiment, which provided concrete evidence that DNA replicated semi-conservatively, as Watson and Crick had suggested.

Also during the 1950s, Delbrück made another shift in his career. Delbrück began studying the fungus *Phycomyces* and its signal transduction, or how it responded to external stimuli like light, electricity, and surrounding objects. Delbrück observed that during *Phycomyces* development, the fungus altered its growth direction and growth rate temporarily in response to different external stimuli. At the time, scientists did not know how the external stimuli were translated into a growth response. Like phage research in the 1930s and 1940s, signal transduction research in *Phycomyces* was also fairly new. According to his biographer, in 1969, Delbrück co-authored a review article on *Phycomyces* to recruit more researchers into the field. In the 1970s, Delbrück also held group meetings and workshops for *Phycomyces* research. Despite the efforts of Delbrück and other scientists, they did not uncover the exact mechanism for how *Phycomyces* responds to stimuli.

Delbrück made many efforts to further science in post-World War II Germany. In 1956, Delbrück co-founded the Institute of Genetics at the University of Cologne in Cologne, Germany, where he served as director and guest professor from 1961 to 1963 during a leave of absence from his job at Caltech. Upon request, Delbrück also served as a consultant at the University of Konstanz in Konstanz, Germany. Furthermore, after World War II and throughout the rest of his life, Delbrück mailed personal copies of scientific journal articles to institutions in Germany that would have otherwise not had access to the information.

Many figures in science and history of science wrote about Delbrück's life through memoirs and biographies. In 1988 Fischer, one of Delbrück's former graduate students, and Lipson compiled Delbrück's autobiographical work and old interviews to write his biography, *Thinking About Science: Max Delbrück and the Origins of Molecular Biology*. Throughout personal recounts of Delbrück's career, many authors highlight Delbrück's influence on other scientists and fields in general. In particular, authors cite the Phage Group, which gained a significant following. Throughout the twenty-six years of phage courses and twenty-one years of phage meetings, the phage group and phage course attracted hundreds of students and researchers from the field of phage genetics. Delbrück also received recognition for his work during his life, receiving many awards and honors. Among those, Delbrück shared the Nobel Prize for Physiology or Medicine with Luria and Alfred Hershey for his work regarding the nature of replication and genetics in phages.

In 1978, doctors diagnosed Delbrück with multiple myeloma, a bone marrow cancer. Despite attempts to treat the cancer using chemotherapy, the cancer eventually led to Delbrück's death on 9 March 1981.

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