

Gertrude Belle Elion (1918-1999)

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Gertrude Belle Elion was a twentieth-century scientist in the US who researched the structure of viral DNA to help develop anti-viral medications. In the 1970s, Elion helped to develop acyclovir, an early anti-viral medication, alongside a team of other researchers. For her work on drug development, Elion was a co-recipient of the 1988 Nobel Prize in Physiology or Medicine, even though she lacked a PhD or MD. Acyclovir was one of the first selective medications to effectively treat herpes simplex virus types 1 and 2, or HSV-1 and HSV-2. Those are common viruses that can be transmitted via close contact or sexual intercourse, and cause sores on the mouth and genitals. The medications that Elion helped develop were also some of the first to specifically inhibit the replication of viral DNA. By creating medications like acyclovir based on her knowledge of chemistry and biology, rather than through trial and error, Elion helped create a new model for drug development, in addition to making an effective treatment for herpes, which afflicts billions of people globally, and can cause life-threatening illness in infants.

Elion was born on 23 January 1918, in New York City, New York. Her mother Bertha Cohen immigrated to the US at fourteen years old from Poland, and her father, Robert Elion, immigrated to the US at twelve years old from Lithuania. Elion's father was a dentist, and the family initially lived in Manhattan in New York City, New York, for seven years of her life. Soon after her younger brother Herbert was born, the family moved to the New York City borough of the Bronx, where she attended Walton High school. Elion described Walton High School as an all-girls school with a good academic curriculum in her memoir *The Quest for a Cure*. Elion writes in her memoir that in 1933, the summer before she began her freshman year of college, her maternal grandfather, with whom she was very close, died of stomach cancer. In a 1997 interview with Mary Ellen Avery, a physician and researcher, Elion shared that watching her grandfather die painfully over the span of multiple months inspired her to major in chemistry in hopes of discovering a cure for cancer.

In 1933, Elion began attending Hunter College in New York City where she majored in chemistry. During the 1929 stock market crash, and the ensuing years of the Great Depression, Elion's father lost much of his fortune, leaving Elion with no money to pay for college. However, she was able to attend Hunter College because it offered free tuition to students with qualifying grades. She graduated in 1937. Because of the Great Depression,

Elion also did not have the funds to attend graduate school, though she applied to several graduate programs to possibly gain an assistantship or a fellowship. Elion started looking for jobs instead, but at the time, it was exceedingly rare for women to work in scientific laboratories. In the interview with Avery, Elion recounted how potential employers told her that her presence in the laboratory would be distracting, and she felt that no one took her seriously. Having struggled to find a laboratory job after earning an undergraduate degree in chemistry, Elion briefly enrolled in secretarial school. She then accepted a three-month long job as a laboratory assistant teaching biochemistry to nurses at the New York Hospital School of Nursing in New York City. After that, Elion found a job, initially working for no pay, as a laboratory assistant for Alexander Galat, a chemist at a pharmaceutical company.

Elion then began graduate school in 1939 at New York University in New York City, where she pursued a master's degree in chemistry. While a graduate student, Elion taught chemistry, physics, and general science as a substitute teacher in New York City high schools. Elion completed her master's degree in 1941 and landed her first job in a laboratory doing quality control checks for a food company. In her autobiography published in the journal *The Oncologist*, Elion explains that she learned a lot about instrumentation, but she eventually grew tired of the repetitive nature of quality control work and began looking for new jobs. Elion briefly worked in a research laboratory for Johnson & Johnson, a company that focused on creating medical supplies, in New Brunswick, New Jersey. In 1944, Elion began working as a chemist at Burroughs Wellcome Co., hereafter Burroughs Wellcome, a pharmaceutical company in Tuckahoe, New York.

At Burroughs Wellcome, Elion worked as a research assistant for George Hitchings, a researcher who studied biochemistry. Hitchings's lab investigated the structure of DNA in pathogens with the aim of creating medications that could interfere with the pathogen's process of DNA replication, thereby treating various diseases. Pathogens are microorganisms, such as bacteria, viruses, and fungi, that have the potential to cause disease. Some viruses can infect human cells, then use the cells' replication mechanisms to create more viruses within the human host. As Hitchings's research assistant, Elion went on to collaborate with Hitchings on numerous scientific papers and research studies throughout her career.

Shortly after going to work for Burroughs Wellcome, in 1944, Elion decided to return to school to pursue a PhD at the Brooklyn Polytechnic Institute in Brooklyn, New York. Elion took classes part-time and at night for two years, working towards her doctorate, until the Dean of the university asked her to quit her job at Burroughs Wellcome and become a full-time student. She instead decided to discontinue her doctoral studies to continue working at the pharmaceutical company. At Burroughs Wellcome, Elion primarily researched the building blocks of DNA under the guidance of Hitchings.

In 1951, Elion synthesized the compound called 6-mercaptopurine, or 6-MP, which demonstrated tumor-shrinking properties and induced cancer remission in later clinical trials. Cancer tampers with the cell division cycle, causing cells to divide uncontrollably, and start to invade and harm other internal structures and tissues. 6-MP inhibits cancer growth by targeting one of the steps of the cell division cycle so that cancerous growths stop dividing and begin to recede. Donald Clarke, a surgeon who worked at Memorial Sloan Kettering Cancer Center in New York City, published a paper in August of 1953, along with Elion, Hitchings, and other colleagues, that demonstrated how 6-MP was able to inhibit tumors in mice. Clarke relayed that some of the tumors even regressed in many of the mice. Later in November of 1953, Joseph H. Burchenal, a physician who researched cancer treatments, who had collaborated with Elion and Hitchings, published results of a clinical trial with colleagues that reported that 6-MP achieved long-term rates of remission in children with leukemia. Later that same year, 6-MP was approved by the US Food and Drug Administration to treat leukemia in children.

Throughout the rest of the 1950s and 1960s, Elion continued to do research with the building blocks of DNA and their potential to treat various health issues, like gout and organ rejection after transplant, publishing numerous papers on her findings. In 1967, Elion became the head of the Department of Experimental Therapy at Burroughs Wellcome. Then in 1970, the company moved to Research Triangle Park, North Carolina, where Elion helped develop acyclovir.

Throughout the 1960s and 1970s, Elion and other researchers at Burroughs Wellcome investigated how to create a medication to treat herpes simplex virus, which eventually led to the development of acyclovir. Prior to the discovery of acyclovir, there were no effective anti-viral treatments available for treating oral and genital herpes, which are caused by the viruses HSV-1 and HSV-2. The two viruses are very similar, with only minor differences in their DNA. HSV-1 typically causes blisters or lesions on the mouth that are colloquially referred to as “cold sores” or “fever blisters.” HSV-2 causes similar lesions on the genitals, such as on the vulva, penis, scrotum, and anus. Usually, HSV-2 is spread via sexual contact, and HSV-1 is typically spread orally, by kissing, and can spread by other forms of close contact, such as sharing eating utensils. But it is also possible for a person to develop genital herpes from HSV-1 or develop oral herpes from HSV-2. The blisters may be raised and fluid-filled and can vary in size. Typically, there is also a burning, itching, or tingling sensation before the blisters appear. While oral and genital herpes do not cause serious illness in most, the lesions can be painful, and can result in negative psychological consequences. According to Adrian Mindel and Caron Marks, researchers who study sexually transmitted infections at The University of Sydney, in Camperdown, Australia, genital herpes can result in psychological conditions such as depression and increased stress. Furthermore, although it is uncommon, mothers can also pass herpes to a newborn child, typically during a vaginal birth. Herpes in newborns can cause severe illness, for example affecting the nervous system and even causing seizures.

Elion's team was investigating how to prevent the spread of herpes lesions by developing a drug that could target the virus's replication mechanisms. HSV-1 and HSV-2 replicate in the body by inserting their DNA into the host's cells and using the host cells' replication machinery to spread the virus. Once a person's cells have been infected with herpes, there is no way to clear the virus from the body. Though there is no cure for herpes, anti-viral medications work to inhibit viral replication by interrupting the replication process, alleviating symptoms and decreasing the likelihood of transmission to others.

At the time that Elion began studying how to create a herpes medication, the scientific community did not accept that it was possible to stop or interfere with viral DNA replication without harming the DNA of the host cell, according to Elion in her memoir *The Quest for a Cure*. But Elion and her colleagues synthesized a compound called 2,6-diaminopurine arabinoside, and in 1969, sent it off to colleague John Bauer, a researcher at the UK branch of Wellcome Research Laboratories who tested the compound and confirmed that it could inhibit HSV replication mechanisms. The discovery of the compound's anti-HSV properties led Elion and colleagues to conduct further research to create a more effective treatment, modifying the initial chemical compound to create acyclovir.

In 1977, Elion and colleagues published a paper discussing the ability of acyclovir, which they referred to as acycloguanosine, to specifically inhibit the replication of HSV-1, while also having low toxicity for normal cells in the body. Then in 1978, Elion and some of the same colleagues published a paper in the academic journal *Nature*, discussing the anti-viral replication properties of acyclovir, the drug's low toxicity for normal cells, and the promising results of acyclovir in animal models. Elion and colleagues tested the efficacy of acyclovir by infecting guinea pigs with HSV-1 and treating one side of the animals with a topical ointment formulation of acyclovir, leaving the other side untreated to act as a control. The researchers found that after three days of treatment, the lesions on the side that was treated with acyclovir healed, while the lesions on the control side were still present. Additionally, acyclovir had low toxicity levels even at doses far greater than what was needed to suppress viral activity in hosts and heal herpes lesions. The 1978 paper highlighted how acyclovir had very low toxicity, did not degrade in the body after administration, and was a possible contender for clinical trials for the treatment of herpes.

In 1982, clinical trials for acyclovir showed that acyclovir decreased the duration of symptoms of genital herpes and expedited healing times for individuals experiencing a first outbreak of genital herpes lesions. In 1982, intravenous and topical acyclovir was approved for public use under the trademark name Zovirax and became available in an oral pill form a few years later. With published papers about the antiviral actions of acyclovir, Elion and her colleagues showed that there was an antiviral medication capable of targeting and interrupting specific components of herpesvirus DNA structure and replication.

Prior to Elion's work, researchers developing drug treatments used a trial-and-error model, by randomly investigating and modifying compounds to produce a drug that could treat illness. Over the course of her career, Elion helped to establish a model of rational drug design, in which researchers attempted to treat diseases by developing compounds that had specific mechanisms with the potential to alter or prevent pathogen proliferation. For example, when Elion and colleagues looked for a treatment for herpes, rather than looking for a compound that just seemed to be effective at decreasing the symptoms of the disease, they developed a compound that could help prevent the disease from replicating at a molecular level. By engineering a medication that targeted the molecular mechanisms of pathogens and worked, she helped spread that new method of approaching drug development.

Less than a decade later, Elion's drug development approach helped her colleagues at Burroughs Wellcome make a newly modified version of azidothymidine, or AZT, one of the first drugs used to treat HIV. HIV, or human immunodeficiency virus, is typically a sexually transmitted virus that can cause AIDS, or acquired immunodeficiency syndrome, a disease that damages the immune system, making it difficult for the body to fight off diseases, with a high mortality rate. In the early 1980s and the late 1990s in the US, an HIV/AIDS epidemic devastated communities. There was at that time no approved cure or treatment to prevent transmission or progression to AIDS. According to Isabella Frascilla, a PhD student studying immunology at Harvard Medical School, in Boston, Massachusetts, Elion mentored her former team at Burroughs Wellcome who published a paper documenting the anti-HIV replication properties of AZT. In 1987, researchers at Burroughs Wellcome conducted a human clinical trial, which demonstrated that AZT decreased AIDS mortality. The method of drug development that Elion and her team originally developed allowed for the creation of AZT and more anti-viral medications in the decades that followed.

Elion earned many honorifics and awards throughout her career, receiving three honorary doctoral degrees in 1969, one from The George Washington University in Washington, DC, another from Brown University in Providence, Rhode Island, and a third from the University of Michigan in Ann Arbor, Michigan. In 1983, Elion retired from her position as the Head of the Department of Experimental Therapy at Burroughs Wellcome and became a Scientist Emeritus and Consultant for the company, an honorary title designating that Elion remained associated with research without conducting any herself. From 1983 to 1984, Elion served as the President of the American Association for Cancer Research, a professional organization of scientists and physicians dedicated to preventing and treating cancer primarily through research. Until 1991, Elion served on the National Cancer Advisory Board, which advises and helps the director of the National Cancer Institute, part of the National Institutes of Health. She also served on numerous committees for the Tropical Disease Research division of the World Health Organization.

In 1988, Elion, along with fellow researchers Hitchings and James Black, won the Nobel Prize in Physiology or Medicine for their efforts in establishing a novel approach to drug development. Following that, Elion received the National Medal of Science from former US President George Bush in 1991 and was the first woman to be inducted into the National Inventors Hall of Fame, according to *The New York Times*. According to Avery, Elion described herself as an avid traveler and lover of classical music, who frequently attended concerts and traveled abroad during her retirement. Not long after retiring, Elion became a Research Professor of Pharmacology and Medicine at Duke University Medical Center in Durham, North Carolina, mentoring medical students to conduct research projects on topics such as tumor biochemistry and pharmacology. Elion mentored Duke medical students for much of the rest of her life.

Elion died on 21 February 1999 in Chapel Hill, North Carolina.

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