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Biography #4 – Gertrude B. Elion (1918 – 1999)

- Gertrude Elion, 1918 – 1999.

Gertrude Belle Elion, who became one of the most prolific inventors of new drugs in the twentieth century, was born in New York City in 1918. Her parents, both immigrants, came from families of scholars and rabbis. Her father, Robert, worked as both a dentist and a stockbroker. The family lived in Manhattan until 1929, when the stock market crash led them to move to the Bronx.

Trudy, as she was known, was shy and an outstanding student with no particular interest in science. She skipped two grades and graduated from Walton High School for girls at age fifteen. Luckily, the City College of New York offered qualified applicants a free and excellent college education. When Elion entered Hunter College, the woman's branch of CCNY, she was undecided on a major. That changed when her beloved grandfather was hospitalised with stomach cancer. Watching him suffer affected the young college student deeply, and she resolved to study science so she could make a contribution against disease. Four years later, she graduated from college as a member of Phi Beta Kappa with highest honours in chemistry.

Just after graduating, Elion met the love of her life, a statistics student named Leonard Canter. Canter called the redheaded Elion, "Brilliant … a vital, fresh, spontaneous, sparkling spirit." They dated for four years, attending plays and concerts and discussing science. Canter respected Elion's ambitions. Determined to get a Ph.D. but lacking money, Elion needed financial aid in the form of a graduate fellowship to continue. Unfortunately, despite her academic achievements, fifteen graduate programmes in chemistry rejected her, largely because she was female. One

university told her, “You’re qualified. But we’ve never had a woman in the laboratory before and we think that it would be a distracting influence.”

Discouraged, Elion enrolled in secretarial school. Soon, though, she got a better offer: two hundred dollars to teach chemistry to nursing students for three months. She took the post. After some hesitation, she also agreed to volunteer in a chemistry lab at Denver Chemical Company. It meant an exhausting day, riding two-and-a-half hours on the subway, rushing through dinner, hurrying off to teacher training classes, and not getting home until ten o’ clock at night. But Elion wrote to Canter, “It’s worth it – if only for the feeling of confidence it gives me.”

Then Canter received a scholarship to study in Paris for a year. While he was gone, Elion’s volunteer position turned into more: the Denver Chemical Company began paying her a salary. Soon, Elion had saved enough money – $450 – to enrol in the graduate chemistry programme at New York University. A morning job as a doctor’s receptionist and occasional assignments as a substitute teacher helped cover her expenses. Later, Elion would advise young women, “Don’t be afraid of hard work. Nothing worthwhile comes easily. Don’t let others discourage you or tell you that you can’t do it. In my day I was told women didn’t go into chemistry. I saw no reason why we couldn’t.”

Canter returned from Paris after graduating from college with a strong academic record, but he too had difficulty finding work. He lost a job offer at Macy’s when the company doctor discovered that he had a heart condition, perhaps rheumatic heart disease. Canter was devastated, but not long afterward he found a job at a stock brokerage. He and Elion became engaged. Then, in November of that year, Canter fell ill with bacterial endocarditis, an infection of the heart valves. Without penicillin, which was not yet available, the disease was incurable. After more than six months of illness, with Elion at his side, Canter died. Elion wrote that he took with him “faith, hope, consolation, beauty.” For many years afterwards, Elion did not date; she never married. Work became everything to her. She later explained that she believed marriage wasn’t an option for a woman who wanted a serious career in science. “If a woman got married, she was often fired; if she had a child, no question – out she’d go. There was no such thing as maternity leave.” After Canter’s death, Elion redirected herself to her goal: harnessing chemistry to cure illness.

Four years later, World War II arrived, pulling so many men out of the labour market that labour opportunities for women blossomed at last. “I don’t know if I would ever have gotten into a research lab without the men being gone,” Elion later reflected. The A&P grocery chain hired her as a quality control officer testing food products. It was chemistry, if only of a very simple kind. Elion checked strawberries for mould, measured the pH of pickle juice, and assessed how egg yolks coloured the mayonnaise. She also learned about quality control.

In 1944, Johnson and Johnson invited her to join a small research lab to help develop *sulfa drugs*. Here at last was her chance to make a real difference. But the new lab closed after only six

months, and when Johnson and Johnson asked her to start testing the strength of surgical thread instead, Elion decided it was time to move again.

This time her dentist father gave her the lead. He had received a free sample of Empirin, a codeine-aspirin mix, from the pharmaceutical company Burroughs Wellcome. Why not try there for a research position? Elion did, and George Hitchings hired her for fifty dollars a week. Elion told herself that she would stay only as long as she kept learning. She stayed nearly forty years, learning organic chemistry, biochemistry, microbiology, cancer medicine, immunology and virology. At first she continued to tale night courses towards a Ph.D. at Brooklyn Polytechnic Institute. Eventually, though, the university gave her a choice: drop her job and attend full time or leave the Ph.D. programme. Elion chose the job.

Thirteen years older than Elion, with a Harvard Ph.D. in biochemistry, Hitchings had been working at Burroughs Wellcome for two years as the company's sole biochemist. Elion's arrival in 1944 marked the beginning of thirty years of remarkably productive collaboration. Most drugs throughout history had been discovered either accidentally or by trial and error, but George Hitchings had a different idea. With enough understanding of biochemical processes, he thought, drugs could be designed more rationally.

When Elion joined the lab in 1944, Hitchings was pursuing an interest in nucleic acids, the building blocks of DNA. Just that year, Oswald Avery had published evidence that DNA is the molecule that carries genetic information. The actual structure of DNA would not be worked out by Watson, Crick and Franklin for another nine years. But Hitchings and Elion reasoned that bacteria and tumour cells, which grow much faster than healthy human cells, would need to build a lot of DNA. Therefore, interfering with DNA synthesis might be a rational approach to attacking cancer or infection.

Hitchings assigned Elion to investigate the class of nucleic acids known as purines. She spent long hours in the library and in the laboratory learning how to synthesise these molecules. If she could design molecules similar to naturally occurring purines, and if these molecules latched onto the enzymes involved in DNA synthesis, then like the wrong key jammed in a lock, they might physically block the enzymes from working on the actual purines needed to build DNA. Thus the new compounds might block the kind of fast cell growth that happens in bacteria or tumours. This class of drugs came to be known as *anti-metabolites* because they interfere with the normal growth and workings, or metabolism, of a cell.

Elion and Hitchings tested Elion's newly synthesised compounds on a bacterium, *Lactobacillus cerei*. In 1948, Elion synthesised diaminopurine, a purine molecule with two $–NH_2$ (amino) groups attached. Diaminopurine blocked growth in *L. cerei*, so Elion and Hitchings shared it with their medical collaborators. Doctors tested the new drug on a handful of adult patients with chronic leukaemia, a massive overgrowth of immature white blood cells that eventually leads to death through infection and bleeding. Although two patients responded well, temporarily losing all signs of leukaemia, two others had to leave the drug trial because of severe vomiting. Still, the

success was enough that the Wellcome group decided to focus the majority of their efforts on cancer.

Next, Elion tried substituting a sulfur atom for an oxygen atom on a purine molecule, creating 6-mercaptopurine, or 6-MP. Here was a drug that routinely sent acute leukaemia in children into remission, increasing the average survival after diagnosis from just a few months to a year or more. Still, all the patients eventually relapsed, an outcome Elion found so heart-breaking that she spent the next six years working to understand everything about how 6-MP worked. She learned that combining 6-MP with other drugs led to longer remissions, sometimes permanent ones. Today, using combination chemotherapy including 6-MP, almost eighty percent of childhood leukaemia victims can be cured.

During this period, Elion wrote a number of papers with herself listed as lead author. Hitchings appeared as senior author, indicating that the work had been done in his laboratory under his general direction. Hitchings trusted Elion's instincts and her productivity, so he tended to give her free rein to follow the directions she chose in her research. It worked well. Elion eventually filed forty-five patents for new drugs.

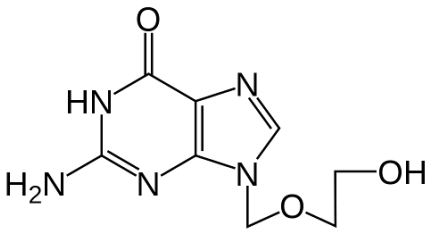
Using the same principle of rational design that had worked so well for 6-MP, Elion went on to develop other drugs. When she synthesised a related compound called 6-thioguanine, or 6-TG, she found that not only did it diminish white blood cell overgrowth, it also seemed to reduce the body's immune response. At that time, surgeons were beginning to experiment with organ transplant for such problems as kidney failure. The problem with transplanted organs was that unless the donor and recipient were identical twins, the recipient's body recognised the transplanted organ as a foreign body and sent white blood cells to reject and destroy it. Elion shared 6-TG with researchers at the Peter Bent Birmingham Hospital in Boston, who found that dogs treated with the drug could accept a transplanted kidney.

The Wellcome team extended and refined their work on 6-TG to discover a new compound, azathioprine. Under the trade name Imuran, the compound successfully supressed the body's tendency to reject newly transplanted organs. Azathioprine also effectively treated the painful and crippling disease rheumatoid arthritis.

The team's remarkable productivity persisted. They developed allopurinol, a drug that decreases the production of uric acid. At high levels in the blood, uric acid can form crystals in joints, causing the painful form of arthritis called gout, or in the kidney, causing kidney stones that can lead to kidney failure. They developed a new drug against malaria called pyrimethamine and a new drug against bacterial infections called trimethoprim.

In 1967, as a result of this stunning run of successes, Hitchings was promoted to vice president for research at Burroughs Wellcome. The new position meant that he no longer did research in the laboratory, and Elion was promoted to head the department of experimental therapy. For years Elion and Hitchings had collaborated closely, publishing papers and filing patents together. Now she was running her own lab with no break in the flow of invention.

Elion returned to a longstanding area of interest, asking whether compounds could be found to treat viral infections. When Howard Schaeffer synthesised a new drug, acyclovir, Elion focused on finding out exactly what it did and how it worked. She discovered that the drug works selectively to inhibit an enzyme used to replicate DNA in the herpes virus. Marketed as Zovirax, acyclovir became a mainstay of treatment for genital and oral herpes, as well as life-threatening conditions such as herpes encephalitis, or herpes infection of the brain. Elion called acyclovir “my crown jewel,” and it became Burroughs Wellcome’s best-selling product. Even more importantly, their success with herpes convinced the Burroughs Wellcome team that they could develop drugs against specific viruses. Later, a team that Elion had trained synthesised azidothymidine, better known as AZT, the first drug effective against HIV and the first specific treatment for people with AIDS.



- The structure of the antiviral drug, acyclovir.

In 1970, the Wellcome Laboratory moved from New York to Research Triangle in North Carolina. Elion moved with it. Still lacking a Ph.D., she became a research professor at Duke University. In 1983, eight years after her mentor Hitchings left Wellcome, Gertrude Elion too officially retired. Although she enjoyed photography, travel, listening to music and attending the ballet and theatre, she also went back to the lab whenever she could.

In her later years, Elion received many honours. Her honorary doctorate from the Polytechnic University of New York was only one of twenty-three honorary degrees. She was elected to the National Academy of Sciences, the Institute of Medicine, and the American Association of Arts and Sciences. She won a National Medal of Science, and she was the first woman inducted into the National Inventors Hall of Fame. In 1988, along with George Hitchings and Sir James Black, she won the Nobel Prize in Physiology and Medicine “for their discoveries of important principles for drug treatment.”

Asked once if she had spent her life aiming for the Nobel Prize, Elion answered, “What we were aiming at was getting people well, and the satisfaction of that is much greater than any prize you can get.” In a box by her bedside she saved her greatest prizes of all – letters of thanks from patients and the parents of patients cured by her inventions. Curing the sick and relieving suffering had always been her goal, but there was more. At the end of her Nobel lecture, Gertrude Elion reminded her audience, “Chemotherapeutic agents are not only ends to themselves, but also serve as tools for unlocking doors and probing Nature’s mysteries.” As for so many women in science, Gertrude Elion found that the sheer fascination of scientific discovery brought a joy all its own.

- Noyce, P. (2015). *Magnificent Minds* (pp. 131-137). Boston, MA: Tumble Home Learning, Inc.