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A NEW APPROACH TO DRUG DEVELOPMENT – THE SUCCESS STORY OF GERTRUDE ELION, A NOBEL LAUREATE

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Gertrude Elion is one of the most prominent figures in the world of science of the 20th century. In 1988, her achievements in the field of pharmacology were recognized at the highest level – she won the Nobel Prize in Physiology or Medicine. Together with George Hitchings and Sir James Black, she received this award “for their discoveries of important principles for drug treatment”, the principles that led to the development of new drugs. Her methods featured an unconventional approach: she sought to create drugs that selectively affected disease-causing cells, thus minimizing side effects. Her research paved the way for what we call today the targeted therapy concept. Elion’s whole life is a success story of a scientist who achieved brilliant results thanks to her tireless work and dedication to science. This article reviews the life and discoveries of Gertrude Elion and explains why her work is still relevant for present-day medicine.

Key words: *Nobel Prize, Gertrude Elion, rational drug design, 6-mercaptopurine, azathioprine, acyclovir.*

Gertrude Belle Elion was born on January 23, 1918, in New York City. Her father, Robert Elion, had immigrated to the United States from Lithuania, and her mother, Bertha Cohen, from Poland. In 1914, Mr. Elion graduated from the New York University School of Dentistry. He married Bertha when she was just 19. For the first seven years of her life, Gertrude lived with her parents in a small apartment next to her father’s dental office. When Gertrude’s brother was born, the family moved to the Bronx, then considered a suburb of New York City. Later, her grandfather, to whom Gertrude was very attached and who devoted much of his time to raising her, also moved there. In 1933, Gertrude’s beloved grandfather died of cancer. This made a strong impression on Gertrude and later strongly motivated her to choose her future profession.

Gertrude graduated from high school at the age of 15. Because her father’s savings had been wiped out by the stock market crash of 1929, her family could not afford tuition fees for her further education, so she had to choose among free schools. She was accepted to the Women’s Hunter College of the



Gertrude B. Elion [1]

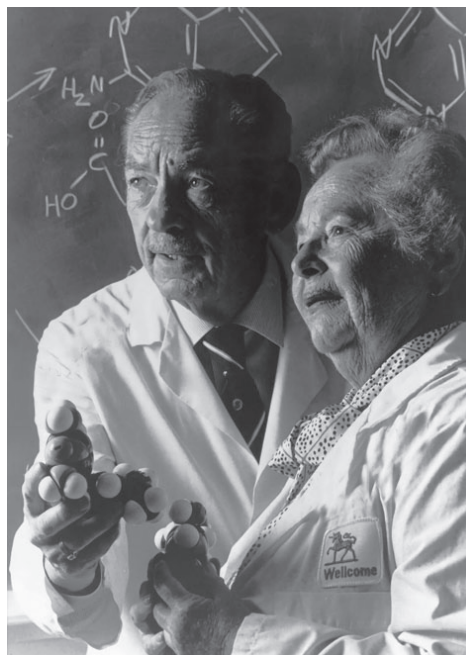
City University of New York. Still grieving for her late grandfather, she decided to study chemistry in the hope of contributing to the fight against cancer. In 1937, Elion graduated summa cum laude from the Hunter College, receiving a bachelor’s degree in chemistry [2].

After graduating from college, Elion dreamt of going to graduate school, but financial constraints prevented her from doing so. At the time, it was difficult for a woman to find work as a chemist. She was 19 when she finally got a short-term job teaching biochemistry at the New York Hospital School of Nursing. Elion later got lucky and found a job as a laboratory assistant. She was paid a mere \$20 a week but could pay for her tuition at New York University, where she was the only female student in her chemistry class. After a year of study at graduate school, Elion completed all the required courses, began teaching chemistry, physics, and general science in New York City high schools, and did research at New York University at night and on weekends. She received her master's degree in chemistry in 1941. By this time, World War II had begun, and there was a shortage of chemists in industrial laboratories, which allowed Elion to get a job as an analytical chemist at a large food company. However, that year brought her not only new opportunities but also a terrible loss – Elion's fiancé died of an infectious disease. If the first antibiotics had been discovered a few years earlier, her life might have taken a different path.

Here's how Elion herself recalls this period of her life: "I think that my social life really took a hiatus in about 1941 – actually before I went to Burroughs Wellcome – because of the death of some-



Chemist Gertrude Elion in her lab coat circa the 1950s [3]



Nobel Prize Winners, George Hitchings and Gertrude Elion, 1988 [2]

one I loved very much. And after that, I really sort of put myself into my work in a way perhaps that I wouldn't have otherwise. I might have gotten married, and it just didn't happen, because the person I was engaged to died of a disease that could have been cured by penicillin, but there was no penicillin. That was another lesson I learned. How important some discoveries could be in life-saving" [2].

Elion later moved to the Johnson and Johnson laboratory in New Jersey, and after the laboratory was disbanded, she was offered a position as an assistant in the research laboratory under the direction of biochemist George Hitchings at Burroughs Wellcome Company (now GlaxoSmithKline). Gertrude considered it a fortunate coincidence that she began working with Dr. George Hitchings who didn't care whether you were a man or a woman, giving everyone equal opportunities [2].

At the time, Gertrude had a master's degree in organic chemistry and little experience, but she was not afraid of hard work, was patient, and quite quickly moved from assistant to organic chemist. She gradually expanded her knowledge, first investigating compounds she synthesized using microbiological tests and eventually studying them using biochemical, immunological, and virological methods [4].

Despite the hard and persistent work in the laboratory, Gertrude did not abandon the idea of getting a doctorate. She entered the doctoral program at the Brooklyn Polytechnic Institute (now the Polytechnic Institute of New York University) for evening courses. After several years of exhausting commuting to work and then to courses, Gertrude made a difficult decision: to keep only her work, quit the courses, and abandon her doctorate. In her biography, she recalls: “Many years later, when I received three honorary doctorates from George Washington University, Brown University, and the University of Michigan, I decided that perhaps this decision was right after all. Unfortunately, neither of my parents lived to see this recognition” [5].

In the postwar years, little was known about DNA biosynthesis, its structure, and the enzymes associated with DNA. In his laboratory, Hitchings sought new, unconventional methods for studying DNA. His approach was to observe differences in nucleic acid metabolism between the simplest, normal human cells and abnormal cells (such as cancer cells, bacteria, and viruses). Hoping to develop drugs that would selectively block the growth of cancer cells, Hitchings assigned Elion to work on purine bases, specifically adenine and guanine, the DNA building blocks. Recalling her work during that period, Elion noted, “Each series of studies was like a mystery story, as we were constantly trying to figure out what the microbiological results meant, with little biochemical information to guide us. Then, in the mid-1950s, work by Greenberg, Buchanan, Kornberg, and others emerged that elucidated the pathways for purine biosynthesis and utilization, and many of our conclusions began to fall into place” [5].

By 1950, Hitchings and Elion had successfully synthesized two compounds – diaminopurine and thioguanine – that prevented purines from entering the metabolic pathway, blocking DNA synthesis and thereby halting cell growth. This led to the first treatment that induced remission in patients with leukemia. Although the new drugs were effective, they had many side effects. In search of a less toxic drug, Elion screened over 100 purine compounds in *L. casei* [6] and found that replacing oxygen with sulfur at the 6-position of guanine and hypoxanthine turned them into inhibitors of purine utilization. This led to the discovery of a purine antagonist, 6-mercaptopurine (Fig. 1). 6-Mercaptopurine (6-MP) and 6-thioguanine (TG) were then tested at Sloan Kettering Institute and found to be active against a wide range of rodent tumors and leukemias [7].

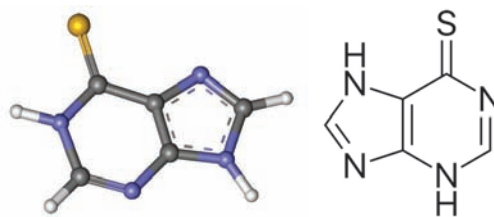


Fig. 1. 6-Mercaptopurine (6-MP) [8]

Approximately two years later, Cancer Research published a paper by David Clarke and colleagues showing that 6-MP had unique activity as an inhibitor of the experimental mouse tumor S-180, prolonging the survival time of mice bearing this tumor and causing complete recovery in a significant number of animals [9].

Following toxicological studies on 6-MP in experimental mammals to understand the risks of its expected therapeutic use and determine its specific cytotoxic effects [10], clinical trials of 6-MP were conducted in children with acute leukemia [11]. The children achieved complete remission but were not cured.

In search of a better outcome, Elion focused on studying the metabolism of 6-MP and TG (Fig. 2). She was able to establish that by combining either 6-MP or TG with other drugs (such as cytosine arabinoside), children with leukemia could be treated more effectively. Today, this method – along with supportive care – is responsible for curing 80 percent of children with leukemia. Thioguanine is also used to treat acute myeloid leukemia (AML) in adults [7].

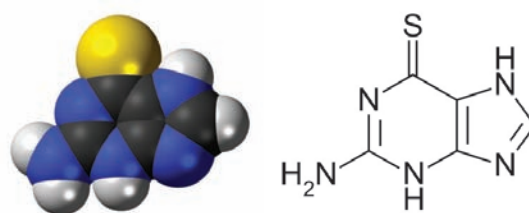


Fig. 2. Thioguanine (TG) [12]

In 1958, Robert Schwartz, in collaboration with William Dameshek, investigated the effect of 6-MP on the immune response, based on the fact that the immunoblastic lymphocyte produced during the immune response closely resembled leukemic lymphocytes. Schwartz showed that when rabbits were given 6-MP for several days, starting from the time of injection of a foreign antigen, such as bovine serum albumin, they did not develop antibodies to that antigen [13].

Schwartz's research inspired Roy Kaln, a young British surgeon, to use 6-MP in kidney transplantation in dogs. He achieved a 44-day survival of a kidney from an unrelated donor in a dog that had been given 6-MP daily [15], which was about four times longer than that of control animals. The results suggested that compounds related to 6-MP might be promising in the search for potent immunosuppressants. Elion suggested that Kaln investigate the recently synthesized (1959) azathioprine (Fig. 3), an imidazole derivative of 6-MP.

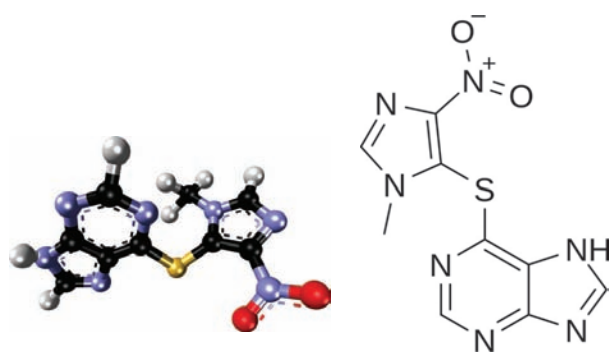


Fig. 3. Azathioprine [14]

Subsequent studies showed that azathioprine, compared with 6-MP, had a more pronounced immunosuppressive effect with less cytostatic activity and prevented rejection of canine kidney homografts [16, 17].

In 1962, successful kidney transplantation in unrelated recipients became a reality in humans with immunosuppressive regimens consisting of azathioprine and prednisone [18]. Eight years later, an even more potent immunosuppressant, cyclosporine, was discovered, making transplanting other organs without rejection a reality for people with weakened immune systems. Today, kidney transplantation is considered therapeutic, not experimental; azathioprine remains the mainstay of this procedure [7] (Nobel Lecture), and the importance of histocompatibility selection is recognized as a key factor in the success of organ and tissue transplantation.

In the 1960s, Hitchings and Elion also made breakthroughs in the fight against infectious diseases by targeting bacterial and viral DNA. This work resulted in pyrimethamine, used to treat malaria, and trimethoprim (Septra), used to treat meningitis, septicemia, and bacterial infections of the urinary and respiratory tracts [19].

Thanks to these stunning results, Hitchings was promoted to vice president of research in 1967,

and Elion was promoted to head of the experimental therapeutics department. The new responsibilities did not prevent her from continuing her research, which included the synthesis of acycloguanosine, also known as acyclovir (Zovirax), an antiviral drug effective against herpes. This discovery refuted the assertions of many biochemists that it was impossible to create drugs that would act both selectively and effectively. As a result of long and painstaking work, Elion proved the opposite.

In her Nobel lecture, Elion noted: "One of the most intriguing aspects of the antiviral activity of acyclovir (ACV) is not only its high potency but its unusual degree of selectivity... It is highly active against herpes simplex virus, types 1 and 2, and varicella zoster virus. It has activity against several other herpes type viruses, e.g., Epstein-Barr virus, pseudorabies, but only slight activity against the human cytomegalovirus (HCMV)".

The study of acyclovir and the convincing evidence of its selective antiviral activity gave Hitchings and Elion an understanding of the rational drug design approach. Her colleagues later developed the AIDS drug azithromycin (AZT) based on this principle. In fact, the development of this drug sealed Elion's fate as a Nobel Prize winner.

She retired in 1983, eight years after Hitchings. Despite her official retirement, she remained active in the scientific world as a consultant to GlaxoSmith-Kline. That same year, she became the president of the American Association for Cancer 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 [20]. Gertrude Elion's name appears on 45 patents.

In 1988, she shared the Nobel Prize in Medicine with her former colleague George Hitchings and fellow researcher Sir James Black. Elion recalled an October morning in 1988: "I was about to go to work and a radio reporter called me to say I had just won the Nobel Prize. And I said, 'Oh, of course. Who put you up to this? This is the kind of joke that I don't find funny at 6:30 in the morning, and you turn around and tell that person I don't find it funny'" [21]. Nevertheless, reporters kept calling, and finally, it was clear: Elion, Hitchings, and Sir James W. Black of the University of London had indeed won the prize in physiology or medicine "for



Gertrude Elion receiving her Nobel Prize from King Carl XVI Gustaf of Sweden, 10 December 1988 [2]

their discoveries of important principles for drug treatment”.

Elion was only the fifth woman to win the Nobel Prize in Medicine, the ninth in science, and one of the few laureates to win the Nobel Prize in Science without a doctorate. It should be noted that by then, she had received honorary doctorates from several universities, including the Polytechnic University of Brooklyn, which had many years earlier encouraged her to keep her job at Burroughs Wellcome.

Further awards and recognition followed the Nobel Prize. In 1990, Elion was elected to the National Academy of Sciences, and in 1991, she received the National Medal of Science, the United States’ highest scientific award. In 1991, she became the first woman inducted into the National Inventors Hall of Fame. She received the National Medal of Science, which was presented to her by President George W. Bush in the White House Rose Garden.

The Nobel Prize made Elion even more in demand as a speaker and spokesperson, and her busy schedule quickly became even busier. Among her numerous duties, Gertrude Elion served as a research professor of medicine and pharmacology at Duke University, supervising third-year medical students in their research in biochemistry and tumor pharmacology. Elion was an incredibly caring and inspiring mentor to undergraduate and graduate students. Elion always adhered to the ethics of scientific research. She encouraged and supported her colleagues in exploring their own ideas and never put her name on a piece of paper simply because the research was being conducted in her lab. Perseverance,

attention to detail, and passion were the most essential ingredients that have always helped Elion in her work and key components of her success.

She preferred to be known simply as a “scientist” rather than a “woman scientist” despite being acutely aware of the difficulties she faced because of her gender. She was the leader of the Glaxo Wellcome (successor to Burroughs Wellcome) program that provided mentoring and scholarships for women studying science. When Burroughs Wellcome gave her \$250,000 for a charity of her choice, she established a scholarship at Hunter College for female graduate students in chemistry [3].

In addition, the Gertrude B. Elion Mentored Medical Student Research Award has been established to provide annual awards of \$10,000. These awards will support female medical students who are interested in health-related research projects [21].

Gertrude Elion was an extremely productive and successful chemist. In addition to treating leukemia, herpes virus, gout, and immune disorders, she also helped develop drugs for arthritis, malaria, and bacterial infections. The rational principles of selective drug design that Elion and Hitchings developed, based on observations of differences in the metabolism of diseased and healthy cells, became the standard in pharmaceutical research. This approach to creating new drugs is still relevant today, so scientists widely use it in the search for cures for many diseases, including cancer, which Elion always hoped to defeat. Currently, one of the main methods of cancer pharmacotherapy is targeted therapy or molecularly targeted therapy. The effectiveness of this therapy lies in the purposeful release of therapeutic substances at the site of the disease while minimizing off-target side effects caused to normal tissues. Targeted therapy involves various strategies, such as monoclonal antibodies, prodrugs, small molecule inhibitors, and antibody-nanoparticle conjugates [22].

When Elion died on February 21, 1999, the head of Glaxo Wellcome insightfully observed: “Gertrude Elion’s love of science was surpassed only by her compassion for people” [3].

In one of her interviews, when asked, “Of all your many accomplishments, what are you most proud of?” Gertrude Elion replied, “I think I’m most proud of the fact that so many drugs have actually been useful in saving lives. I’ve met people whose lives have been saved, and the satisfaction you get when someone comes up and says, ‘My child had

acute leukemia, and your drug saved him'. Or, 'My little girl had herpes encephalitis, and now she's cured, she's back in school. She's doing very well. People have told me she might be mentally ill, but she's not". I meet people who have had kidney transplants for 20 years who are still taking the drug. And I don't think anything else that happens to you can compare to that kind of satisfaction' [2].

Gertrude Elion is a brilliant example of a scientist whose dedication to science, sharp mind, and outstanding achievements inspire generations of researchers worldwide.

НОВИЙ ПІДХІД ДО СТВОРЕННЯ ЛІКІВ – ІСТОРІЯ УСПІХУ ЛАУРЕАТКИ НОБЕЛІВСЬКОЇ ПРЕМІЇ ГЕРТРУДИ ЕЛІОН

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Гертруда Еліон – одна з найвидатніших фігур у світі науки ХХ століття. У 1988 році її досягнення у сфері фармакології були визнані на найвищому рівні – вона стала лауреаткою Нобелівської премії з фізіології та медицини. Разом із Джорджем Гітчінгсом і сером Джеймсом Блеком вона отримала цю нагороду «за їхні відкриття важливих принципів медикаментозного лікування» – принципів, які привели до розробки нових ліків. Її методи відрізнялися нетрадиційним підходом: вона прагнула створювати ліки, які вибірково впливають на хвороботворні клітини, мінімізуючи побічні ефекти. Її дослідження проклали шлях до концепції, яку ми сьогодні називаємо таргетною терапією. Все життя Еліон – це історія успіху науковиці, яка завдяки своїй невпинній праці та відданості науці досягла блискучих результатів. Ця стаття знайомить з життям і відкриттями Гертруди Еліон та пояснює, чому її робота досі актуальна для сучасної медицини.

Ключові слова: Нобелівська премія, Гертруда Еліон, раціональний дизайн ліків, 6-меркаптопурин, азатіопірин, ацикловір.

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