

Editorial

# Gertrude Belle Elion, Chemist and Pharmacologist, Discoverer of Highly Relevant Active Substances

Juan Núñez Valdés <sup>1,\*</sup> , Fernando de Pablos Pons <sup>2</sup>  and Antonio Ramos Carrillo <sup>3</sup> <sup>1</sup> Department of Geometry and Topology, Faculty of Mathematics, University of Seville, 41012 Seville, Spain<sup>2</sup> Department of Analytical Chemistry, Faculty of Chemistry, University of Seville, 41012 Seville, Spain; fpablos@us.es<sup>3</sup> Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Seville, 41012 Seville, Spain; antonioramos@us.es

\* Correspondence: jnvaldes@us.es

**Abstract:** Gertrude Belle Elion was a woman who had to overcome many difficulties to achieve her dream of studying to be able to cure illnesses, especially those of the heart. These difficulties were imposed both by the limited economic resources of herself and her family, which did not allow her to pay the academic fees of the university in which she wanted to enroll, as well as gender, since she also had to fight against inequalities of that type prevalent in the society of her time. However, and despite these obstacles, she managed to graduate in Chemistry, based on interest, effort and tenacity, and later began a research career full of successes, which led her to discover relevant active substances which allow her to be awarded the Nobel Prize in Physiology or Medicine in 1988. This article presents the most relevant features of her personal and professional life and completes previous biographies about her life. Its main objective is to reintroduce her to society and put her as a reference to other people. The methodology followed has been the search for those data about her life and work that would allow completing the previous existing biographies about her.

**Keywords:** Gertrude Belle Elion; active substances in pharmacy; female chemists; Nobel Prize in Physiology or Medicine



**Citation:** Núñez Valdés, J.; de Pablos Pons, F.; Ramos Carrillo, A. Gertrude Belle Elion, Chemist and Pharmacologist, Discoverer of Highly Relevant Active Substances. *Foundations* **2022**, *2*, 443–456.

<https://doi.org/10.3390/foundations2020029>

Received: 28 April 2022

Accepted: 29 April 2022

Published: 6 May 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

The Nobel Prize in Physiology or Medicine is awarded annually by Sweden's Karolinska Institute to "scientists and physicians who stand out for their contributions in the field of physiology or medicine". It is one of the five modalities of the Nobel prizes, established in the will of Alfred Nobel in 1895, and which are given to all those people or entities that make notable contributions in chemistry, physics, literature, peace and physiology or medicine.

Up to and including 1987, there were 144 winners of the Nobel Prize in that category (in some years it was not awarded, and in others there was more than one winner), only 4 of them being women: Gerty Theresa Cori (in 1947, together with Carl Ferdinand Cori, for their discovery of the mechanism of the catalytic conversion of glycogen), Rosalyn Yalow (in 1977, together with Roger Guillemin and Andrew V. Schally, for the development of peptide hormone radioimmunoassays), Barbara McClintock (in 1983, for her discovery of mobile genetic elements) and Rita Levi-Montalcini (in 1986, together with Stanley Cohen, for her discoveries of growth factors).

In 1988, Gertrude Belle Elion was awarded the Nobel Prize in Physiology or Medicine, together with George Herbert Hitchings and Sir James Whyte Black, for "discoveries of important new principles of drug treatment". Therefore, she was the fifth female Nobel laureate in Medicine and the ninth in science in general and one of only a handful of laureates without a doctoral degree. She was the only woman honored with a Nobel Prize that year.

This paper is devoted to show the biography of this woman with the main objective of completing the biographies already existing in the literature about her with novel data from the authors' own research in order to introduce her as a reference to society and as an example of a woman who had to overcome numerous difficulties throughout her life, mainly economic but also sexist, to be able to achieve what she yearned for from the moment her grandfather died and, later, her boyfriend: try to cure illnesses, particularly those of the heart.

## 2. Materials and Methods

The methodology followed in the article has consisted of searching for information on the figure of Gertrude Belle Elion in all kinds of sources, fundamentally primary, in archives and records, both bibliographic and digital, with the aim of highlighting all the relevant aspects of her life that are not contemplated in the existing previous biographies about her.

Efforts have been made to emphasize those most important aspects, both of her life and of her professional work, which led her to be awarded the Nobel Prize in Physiology or Medicine due to the important discoveries she made in the field of pharmacological products.

## 3. Results: Gertrude Belle Elion: Her Biography

Gertrude Belle Elion (Figure 1), the daughter of Jewish immigrants, was born in a poor neighborhood in New York on 23 January 1918. Her family, very humble and low-income, was formed by her father, Robert Elion, a Lithuania Jewish immigrant and a dentist and her mother, Bertha Cohen, a housewife of Polish ascent. The family lost almost all of their wealth after the Wall Street Crash of 1929.

Gertrude Belle Elion, Trudy as she was familiarly known [1], was an excellent student who graduated from Walton High School. In that time, 1933, when she was only 15 years old, 2 years younger than required to start undergraduate studies, her grandfather, with whom she was very close, died of stomach cancer. She accompanied him during his last moments.



**Figure 1.** Gertrude Belle Elion, as a child, with her mother in 1921. Source: [2].

The event of her grandfather's death motivated her to try to cure the disease that took his life, and for this reason, she decided to study a career in science and medicine in college, choosing Chemistry. In this way, she first entered those studies at Hunter College, a public university in her city. She remained there until she graduated in 1937 [2]. She was Phi Beta Kappa at Hunter College, which she was able to attend for free due to her grades, graduating summa cum laude in 1937 with a degree in Chemistry. In fact, she always had a great interest in acquiring new knowledge. Rosich and Bosch (members of the Dr. Antoni

Esteve Foundation in Spain) affirmed that *“she was a person with great determination and perseverance, which allowed her to face the prejudices against her condition as a woman”* [2].

Once these studies were completed and to continue with other superiors, the next step was to go to the University of New York, but she did not have the financial resources to do so, since the financial crash of 1929 had left her family in a very bad economic situation, and they could not afford the payment of her academic fees. However, she was not discouraged, and her enthusiasm for research led her to work first for free, teaching biochemistry to nurses at the School of Nursing in New York for three months, and later for a paltry salary of USD 20 a week, as a chemist’s assistant (A chemist was looking for someone to work as a lab assistant, and she accepted immediately, thinking that the job would be a good experience for her. In fact, she had applied for several teaching assistant positions to obtain the necessary funds, but none were accepted). She alternated this work with teaching: she was a professor of chemistry and physics at several higher education centers, such as Duke University or the New York School of Nursing [3]. At Duke University, she worked as an Adjunct Professor of Pharmacology and of Experimental Medicine from 1971 to 1983 and a Research Professor from 1983 to 1999. During her time at that University, she focused on mentoring medical and graduate students. In fact, she published more than 25 papers with the students she mentored at Duke [4].

Finally, the savings that she was able to achieve, although scarce, and her brilliant record allowed her to enroll in a postgraduate degree in Chemistry at the University of New York in 1939, which, although it had academic fees, also allowed free enrollment under those conditions.

Gertrude Belle Elion (Figure 2) earned her M.Sc. in Chemistry in 1941 [5], being the only woman in her class during her entire degree, although that fact did not make her feel strange [6]. In an interview after receiving her Nobel Prize, she stated that *she believed the sole reason she was able to further her education as a young female was because she was able to attend Hunter College for free*. Her 15 financial aid applications for graduate school were turned down due to gender bias, so she had to enroll in a secretarial school, where she attended only six weeks before she found a job.



**Figure 2.** Gertrude Belle Elion, as a young girl. Source: [3].

The economic difficulties that she had to overcome to get earn degree did not end when she left the University. Employment was very scarce in the midst of the economic crisis and in a much more noticeable way for women, in particular for women scientists, who had very difficult access to the world of work at that time. Rosich and Bosch stated in [2] that *“in a job interview, she was rejected for fear of distracting the attention of the workers*

*who, of course, were all men*". However, she was able to combine teaching with a small job as a laboratory assistant to pay for the postgraduate studies she wanted to pursue [2].

In 1939, Gertrude Belle Elion began a master's degree in Chemistry at New York University, also being the only woman to enroll. She could only study at night and on weekends since in order to pay for that master's she worked in the mornings as a receptionist in a doctor's office and in the afternoons as a Chemistry and Physics teacher. However, she managed to finish her master's degree in 1941 [2], this being the highest academic degree she would achieve.

At Hunter College, Gertrude Belle Elion had met Leonard Canter, an outstanding statistics student at the City College of New York. They planned to marry, but Leonard became ill and died on 25 June 1941 of bacterial endocarditis (an infection of his heart valves that only a few years later could already be properly treated with the discovery of penicillin by Alexander Fleming). Again, that death, along with the previous one of her grandfather, made her work even harder to try to find a treatment for those diseases that caused so many deaths, in particular the ones of those two people very dear to her [2].

Although World War II brought many horrors, it allowed women to apply for jobs that were previously inaccessible for them because they were held by men, many of whom, voluntarily or forcibly, entered the army. That was the reason that Gertrude Belle Elion could start working as a food quality supervisor at A&P supermarkets, a food company, where she stayed for a year and a half, as well as in the laboratories of several companies testing the acidity of pickles and the color of egg yolk going into mayonnaise, where at least she was able to learn a lot about the laboratory instruments, even though these were quality control works and not related to her research at all. Later, after seeking employment in many employment agencies, she went on to hold a research position at Johnson & Johnson [2], one of the best-known pharmaceutical companies in the world.

Johnson & Johnson was founded by the three Johnson brothers, Robert, James and Edward, in 1886 in New Brunswick, New Jersey. Initially, it focused on the preparation of bandages, sterile sutures, antiseptics and baby products. Its first aid kits, originally prepared for railroad workers, later became a staple in almost every home. It also sold women's health products, including sanitary protection products and maternity kits with first aid products to help home births.

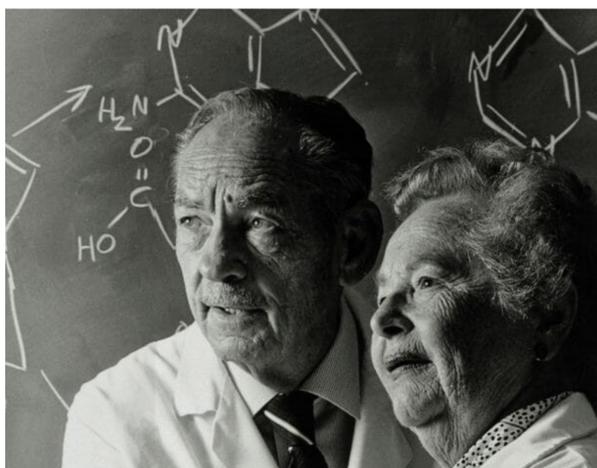
In 1944, Gertrude Belle Elion moved from that company to another no less important one: the Burroughs-Wellcome pharmaceutical company, founded in 1880 in England (now called GlaxoSmithKline), which became the sixth largest pharmaceutical company in the world according to the classification of the Forbes magazine in 2014. At that company, she went on to work as an assistant to George Herbert Hitchings in the lab, going from being an expert in organic chemistry to delving into fields closely related to pharmacy, such as biochemistry, immunology and pharmacology [6].

Gertrude Belle Elion and George Herbert Hitchings hypothesized at the Burroughs-Wellcome laboratory that if the cells of living beings needed to synthesize nucleic acids, the growth of bacteria, parasites or cancer cells, whose metabolism is slow, could somehow be blocked faster than that of healthy cells, introducing the wrong pieces into the body (Remember that, at that time, there was still no very detailed knowledge of nucleic acids, since the structure of the double helix was only discovered in 1953). This theory, known as the "*antimetabolite theory*", required in-depth studies of chemical synthesis. The key was to make molecules very similar to the pyrimidine and purine bases of nucleic acids but with some structural error that managed to stop their metabolism. To do this, Gertrude Belle Elion and George Herbert Hitchings used the biochemical differences between normal human cells and pathogenic (disease-causing agents) human cells to design drugs that could eliminate or inhibit the reproduction of particular pathogens without damaging host cells. Thus, they passed from the "trial and error test" to a much more rational, direct and, in the long run, effective strategy to design drugs that could eliminate or inhibit the reproduction of particular pathogens without damaging host cells [2].

After two years of working in the Burroughs-Wellcome laboratory, Gertrude Belle Elion had to choose between continuing her doctoral studies and her job at the pharmaceutical company. Due to pressure from the dean of the Brooklyn Polytechnic Institute, where she was completing her thesis part-time, she decided to abandon those studies to continue her work in the laboratory with Hitchings (Figures 3 and 4) dedicated to the ingenious task of synthesizing antimetabolites



**Figure 3.** Gertrude Belle Elion with George Herbert Hitchings in the Laboratory. Source: [7].

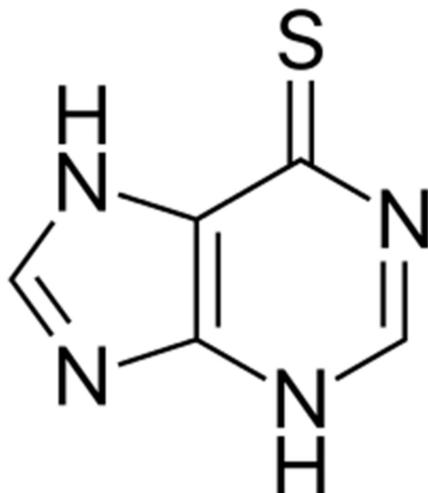


**Figure 4.** Gertrude Belle Elion with George Herbert Hitchings in the Laboratory. Source: Biblioteca Digital de la Universidad de Alcalá de Henares (Spain), respectively.

Paradoxically, years later, Gertrude Belle Elion would become a Nobel Prize winner without having obtained a doctorate. Although she never obtained the official title of doctor, she was later recognized with three honorary doctorates by George Washington University, Brown University, Michigan University and New York University Tandon School of Engineering (then Polytechnic University of New York) and an honorary S.D. degree from Harvard University in 1998 [6].

The work of both scientists bore its first fruits at the end of the 1940s when they managed to show that “the inhibition of DNA synthesis in tumor cells, bacteria and viruses could be achieved using analogs of nucleic acids” (Rosich and Bosch in [2]). In 1948, Gertrude Belle Elion synthesized *diaminopurine* for the first time, a compound that inhibited the growth of *Lactobacillus Casei* by incorporating it into DNA strands. Clinical studies of this compound showed encouraging results in the treatment of leukemia, although it also had contraindications, as side effects related to nausea and vomiting were observed. Three years later, George Herbert Hitchings and Gertrude Belle Elion synthesized two derivatives

that inhibit purine biosynthesis: *6-thioguanine* and *6-mercaptopurine* (Figure 5). As explained by Joseph Eladi Baños, Professor of Pharmacology at Pompeu Fabra University (Spain), “especially important was *mercaptopurin*”, as it was considered the first effective anticancer drug in the fight against childhood leukemia, which allowed the increased survival of children from 3 to 12 months. Professor Baños continued pointing out that [2]:



**Figure 5.** The Mercaptopurine molecule, one of Gertrude Belle Elion’s discoveries. Source: [8].

*Only in this way we can we understand that she went from being a mere assistant to an exceptional collaborator. They took ideas from other authors, but both managed to crystallize their collaboration in effective and relatively safe drugs.*

These results allowed for a quick approval of the drug by the US Food and Drug Administration (FDA for its acronym in English). The synthesis of *mercaptopurine* undoubtedly marked a before and after in the history of medicine: the compound is currently used in combination with other drugs in patients with acute lymphoblastic leukemia. With this, the prognosis of this disease is much more favorable, since it remits around 80% of cases, and children who overcome it reach adulthood [2].

Gertrude Belle Elion’s work led to the emergence of healing therapies. Thus, in 1950 *pyrimethamine* arrived, a successful drug in the treatment of malaria. Then came trimethoprim or azathioprine, the last immunosuppressant being very effective in patients receiving transplants. Her results also greatly helped to combat other diseases, such as gout, rheumatoid arthritis or leishmaniasis [2].

When George Herbert Hitchings retired in 1967, Gertrude Belle Elion (Figure 6) continued to work at the head of the research team as the Head of the Department of Experimental Therapy at Borroughs-Wellcome, arriving months later at the discovery of *acyclovir*, considered to be the first antiviral drug that blocks the replication of the herpes viruses. She also worked for the National Cancer Institute, the American Association for Cancer Research and the World Health Organization [9]. In any case, her greatest research, for which she was awarded the Nobel Prize in Physiology or Medicine in 1988, together with George Herbert Hitchings (with whom she worked with for 40 years) and James Whyte Black, consisted, as already indicated, of the study of the biochemical differences between normal and pathogenic human cells to design drugs that could eliminate or inhibit the reproduction of particular pathogens without damaging the host cells.



**Figure 6.** Gertrude Belle Elion at the time of winning the Nobel Prize. Source: [10].

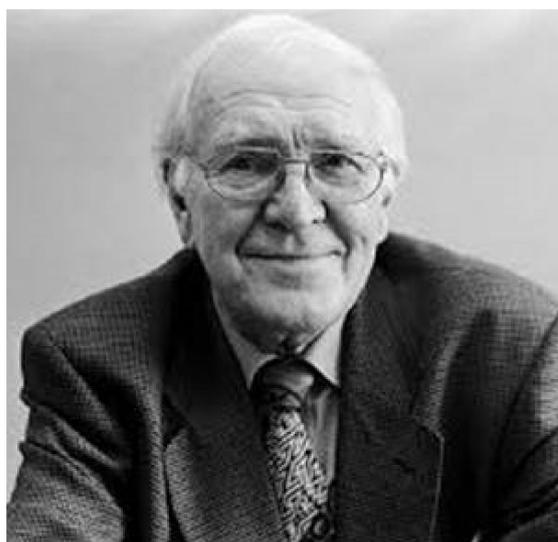
For the purposes of having a better understanding of the fact that this Nobel Prize was awarded jointly, it is convenient to indicate that George Herbert Hitchings (Figure 7), born on 18 April 1905 and died on 27 February 1998, had a bachelor's and doctorate in Chemistry at Brown and Washington Universities, respectively.



**Figure 7.** George Herbert Hitchings at the time of winning the Nobel Prize. Source: [11].

He joined Borrough-Wellcome in 1942, where he was director of the research department and later professor of pharmacology at Brown, Duke and North Carolina Universities. His main works dealt with the metabolism of nucleic acids in order to find differences in the metabolism between tumor and normal cells, as well as between bacteria and viruses. For this work, he was awarded the Nobel Prize in Physiology or Medicine in 1988, which he shared with James Whyte Black and Gertrude Belle Elion herself, for the following reason: *“the discovery of important principles in drug therapy,” especially in the field of chemotherapy*”.

For his part, James Whyte Black (Figure 8), born in Uddingston, Scotland, on 14 June 1924 and died in the same city on 21 March 2010, graduated in Medicine in 1946 from the University of St. Andrews. In 1950, back in Scotland, he launched the Veterinary School at the University of Glasgow, establishing a department of Physiology. He alternated his academic career with various jobs in the pharmaceutical industry. He worked in several of the most important industries in this sector and was appointed professor of pharmacology at University College and King's College London. He discovered *propranolol*, thereby revolutionizing the medical treatment of angina pectoris (which is currently considered one of the most important contributions to medicine and clinical pharmacology of the 20th century) and *cimetidine* (see Appendix A), so frequently applied and used in the current treatment of duodenal and stomach ulcers. In 1981, he was appointed Knight (Sir) of the Order of Merit by Queen Elizabeth II, this being the highest decoration that can be awarded in that country.



**Figure 8.** James Whyte Black at the time of the Nobel Prize. Source: [12].

Rather than relying on trial-and-error, Gertrude Belle Elion and George Herbert Hitchings (Figures 9 and 10) discovered new drugs using rational drug design, which used the differences in biochemistry and metabolism between normal human cells and pathogens (disease-causing agents such as cancer cells, protozoa, bacteria and viruses) to design drugs that could kill or inhibit the reproduction of particular pathogens without harming human cells. The drugs they developed are used to treat a variety of maladies, such as leukemia, malaria, lupus, hepatitis, arthritis, gout, organ transplant rejection (azathioprine), as well as herpes (acyclovir, which was the first selective and effective drug of its kind). Most of Elion's early work came from the use and development of purine derivatives. Her research contributed to the development of the following active pharmacological substances [7] (see Appendix A):

- Mercaptopurine (Purinethol), the first treatment for leukemia, also used in organ transplantation.
- Azathioprine (Imuran), the first immuno-suppressive agent, used for organ transplants.
- Allopurinol (Zyloprim), for gout.
- Pyrimethamine (Daraprim), for malaria.
- Trimethoprim (Proloprim, Monoprim, others) [12], for meningitis, sepsis, and bacterial infections of the urinary and respiratory tracts.
- Acyclovir (Zovirax), for viral herpes.
- Nelarabine, for cancer treatment.



**Figure 9.** Gertrude Belle Elion working in the lab. Source: [7].



**Figure 10.** Gertrude Belle Elion and George Herbert Hitchings in the lab in 1948. Source: [7].

Among Gertrude Belle Elion's publications of her research, which she carried out individually or in collaboration with other researchers, particularly with George Herbert Hitchings, the following can be cited:

- Elion GB; Hitchings GH; Vanderwerff H (1951). Antagonists of Nucleic itchingsd Derivatives. VI. Purines. *Journal of Biological Chemistry*. 192 (2): 505–518.
- Elion GB (1975). Interaction of Anticancer Drugs with Enzymes. *Pharmacological Basis of Cancer Chemotherapy*.
- Elion, G. (1989). The Purine Path to Chemotherapy. *Science*. 244 (4900): 41–47.
- Elion, G. B.; Furman, P. A.; Fyfe, J. A.; Miranda, P. d.; Beauchamp, L.; Schaeffer, H. J. (1977). Selectivity of Action of an Antiherpetic Agent, 9-(2-hydroxyethoxymethyl) guanine. *Proceedings of the National Academy of Sciences*. 74 (12): 5716–5720.
- Elion, Gertrude B.; Hitchings, George H. (1955). The Synthesis of 6-Thioguanine. *Journal of the American Chemical Society*. 77 (6): 1676.

Not only was Gertrude Belle Elion (Figure 11) awarded the Nobel Prize, although it was the most important and the one that made her better known by society, she also received the Garvan-Olin Medal (1968), the Sloan-Kettering Institute Judd Award (1983), the American Chemical Society Distinguished Chemist Award (1985), the American Academy of Achievement's Golden Plate Award (1989), the American Association of Cancer Research Cain Award (1985), the American Cancer Society Medal of Honor (1990), the National Medal of Science (1991) and the Lemelson-MIT Lifetime Achievement Award (1997). In 1991, Elion became the first woman to be inducted into the National Inventors Hall of Fame. She was inducted into the National Women's Hall of Fame also in 1991. In 1992, she was

elected to the Engineering and Science Hall of Fame. She was elected a Foreign Member of the Royal Society in 1995 [13].



**Figure 11.** Gertrude Belle Elion. Source: [14].

She was also elected a member of the National Academy of Sciences in 1990, a member of the Institute of Medicine in 1991 and a Fellow of the American Academy of Arts and Sciences also in 1991.

Regarding her personal life, Gertrude Belle Elion affirmed that “*her work was her life*”, but she also enjoyed photography and travel, both products of her curiosity about life. She also enjoyed opera, ballet and theater. Although she never married or had children, she really enjoyed being the “*favorite aunt*” to her brother’s children. Her brother, whom she was close with, married and had two sons and a daughter that she took pride in being able to watch grow. She listed her hobbies as photography, travel, opera and ballet and listening to music [15].

After Burroughs-Wellcome moved to Research Triangle Park in North Carolina, she moved to the nearby Chapel Hill and retired in 1983 from Burroughs-Wellcome to spend more time traveling and attending the opera.

However, despite her retirement, she never gave up her passion for science. She continued as an emeritus researcher, helping in the development of the first AIDS drug: *zidovudine* [2] (see Appendix A). Other passions of hers during this time was encouraging other women to pursue a career in science [16].

Gertrude Belle Elion (Figure 12), who had fought so hard in her quest to discover new drugs that would prevent and cure major diseases, especially heart disease, died of natural causes in North Carolina in 1999, at the age of 81 [17], after having been single all her life and proud of having fulfilled a secret promise she made to her grandfather once he passed away. In Wikipedia, she is cataloged as a “biologist, chemist, biochemist, pharmacologist, pharmacist and teacher”, although there is no evidence in any other bibliographical source that she obtained these degrees, except for chemistry. Several authors have written about her, among them, Altman (1999) [18], Avery (2000) [19], Koenig (2006) [20] and MacBain (2004) [21], for instance.



**Figure 12.** Gertrude Belle Elion. Source: [13].

#### 4. Discussion

This article completes the existing biographies in the literature on the figure of Gertrude Belle Elion, a woman who, without a doubt, can be considered a true reference and model to be followed by all those other women who are currently dedicating themselves to pharmacological research. As can be seen in her biography, this woman had to overcome numerous difficulties of all kinds, both economic and sexist, to follow a vocation that came from feeling that she could not do anything in the face of the sad death of her grandfather due to a heart condition, for which adequate drugs were not yet available to treat. The death of the person with whom she was going to share her life to the same type of ailment motivated her even more in her desire to investigate these drugs with more desire, effort and tenacity.

There is no doubt that all the pharmacological products that she helped to discover, such as mercaptopurine for leukemia, also used in organ transplantation; azathioprine for organ transplants; allopurinol for gout; pyrimethamine for malaria; trimethoprim, for meningitis, sepsis and bacterial infections of the urinary and respiratory tracts; acyclovir for viral herpes; and nelarabine for cancer treatment, among others, are currently widely used in the treatment of various diseases. This woman's contributions to society have been very relevant, and for these discoveries alone, she deserves to be much better known than she is today. Think, for example, of the number of human lives that Alexander Fleming saved with his discovery of penicillin and the just fame that he has achieved for it. Without wishing to establish any comparison between both of them, given the different circumstances and differences between the times and the societies in which they lived, it is strange, however, the infinite degree of knowledge that today's society has on Fleming compared to that on her, despite the significance of her discoveries.

For all these reasons, the authors believe that this article can be a first step to continue researching the figure of Gertrude Belle Elion in the future (and on many other women who also made great discoveries but who are also practically unknown to everyone) and place her in the place she deserves for her invaluable contributions to society.

Among those women who also dedicated their lives to research to try to cure diseases, one could mention, for example, Gabriela Morreale (1930–2017), who was the discoverer of the heel prick test for the early detection of congenital and metabolic diseases and

neurological disorders in babies, thanks to which it is possible to prevent some 150 children a year from suffering from mental retardation as a result of congenital hypothyroidism; or Patricia Bath (1942–2019), who, in 1976, was one of the founders of the American Institute for the Prevention of Blindness, which established within its statutes that “vision is a basic human right” and that in 1981, being an ophthalmological surgeon, worked to improve the techniques used in cataract surgery, presenting in 1986 the laserphaco, an instrument that she patented in 1986, which dissolves cataracts quickly and painlessly; or Elizabeth Lee Hazen (1885–1975) and Rachel Fuller Brown (1898–1980), who discovered *nystatin*, the first useful antifungal antibiotic, currently known commercially as “Mycostatin”, which allowed the treatment of skin and mucosal infections caused by fungi in dangerous areas of the body.

Allow us, therefore, to finish the biography of this exceptional scientist, Gertrude Belle Elion, 1 of the 58 women who have won the Nobel Prize in any of their modalities up to the present, by showing as a tribute to her figure some of her phrases that she quotes in her autobiography, which summarize her life, her studies, her work, her character and everything that made her deserve to be highly recognized by society for all that she contributed [22]

- *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 time they told me that women did not enter chemistry. I didn't see any reason why we couldn't.*
- *No one took me seriously. They wondered why in the world I wanted to be a chemist when no women were doing it. The world was not waiting for me.*
- *The Nobel Prize is fine, but the drugs I have developed are rewards in themselves.*
- *I had fallen in love with a young man . . . and we were planning to get married. And then he died of subacute bacterial endocarditis . . . Two years later, with the advent of penicillin, he would have been saved. It reinforced in my mind the importance of scientific discovery.*
- *People often ask me [if] the Nobel Prize [was] what you were looking for all your life, and I say that would be crazy. Nobody would aspire to a Nobel Prize because, if you didn't get it, you would lose your whole life. Our goal was to make people feel good, and the satisfaction of that is far greater than any award you can get.*
- *I didn't have a specific bent toward science until my grandfather, who died that summer of stomach cancer. . . . I decided that no one should suffer so much.*
- *It is important to go to work that you would like to do. So it doesn't look like work. Sometimes you feel like it's almost too good to be true that someone will pay you to have fun. I have been very fortunate that my work has led to useful medicines for a variety of serious illnesses. The thrill of seeing people get better who might otherwise have died from diseases like leukemia, kidney failure, and herpes virus encephalitis cannot be described in words.*
- *That was the turning point. It was as if the signal was there: 'This is the disease we will have to work against'. I never really stopped to think about anything else. It was that sudden.*
- *I think it is very valuable for a doctor to learn to investigate, to learn to approach research, something that there is no time to teach them in medical school. They don't really learn how to approach a problem, and yet diagnosis is a problem; and I think that year dedicated to research is extremely valuable to them.*

**Author Contributions:** J.N.V., F.d.P.P. and A.R.C. have contributed equally to the preparation and writing of this article. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## Appendix A

In order to be better understood by the reader, we indicate in this Appendix the main characteristics of the pharmacologically active substances discovered by or with the assistance of Gertrude Belle Elion. The following data are taken from the Spanish Agency for Medicines and Health Products.

Mercaptopurine, also called 6-mercaptopurine or 6-MP for short, is an immunosuppressive drug used in the treatment of some types of cancer, mainly acute lymphocytic leukemia. It is also used to treat other diseases, including ulcerative colitis and Crohn's disease. Its main characteristics are the following: Formula:  $C_5H_4N_4S$  and CAS Number: 50-44-2; Molar mass: 152.177 g/mol; and Boiling point: 471 °C (the CAS Number is a unique and unambiguous identifier of a specific substance that ensures clear communication, and with the help of CAS (acronym of American Chemical Society) scientists, connects all available data and research on that substance).

Azathioprine is a prodrug related to 6-mercaptopurine. Both are usually jointly called thiopurines and are used as immunosuppressive agents, currently preferably in the treatment of diseases in which the immune system is activated in the wrong way, thus becoming necessary to modulate it. Some examples are Crohn's disease, ulcerative colitis, autoimmune hepatitis, multiple sclerosis, systemic lupus erythematosus and other diseases. In previous years, it was a basic drug in organ transplants, associated with steroids or other agents. Currently, it is used less in this indication, but it is still important. It was the first medication that was shown to be effective in increasing survival in kidney, heart and liver transplants.

Allopurinol is a chemical compound used as a medicine against hyperuricemia (excess uric acid in blood plasma) and its complications, such as gout. Its formula is  $C_5H_4N_4O$ , and its CAS Number is 315-30-0.

Pyrimethamine (Daraprim) is a drug used to treat protozoan infections. It is used primarily for the treatment and prophylaxis of malaria and is also used in combination with *sulfadiazine* in the treatment of patients with *Toxoplasma gondii* infection (toxoplasmosis) in immunocompromised patients, such as in HIV-positive individuals, and in the treatment of toxoplasmosis during the second and third trimesters of pregnancy. Its formula is  $C_{12}H_{13}C_{11}N_4$ , and its CAS Number is 58-14-0.

Trimethoprim is a bacteriostatic antibiotic derived from trimethoxybenzylpyrimidine and used almost exclusively in the treatment of urinary tract infections. It belongs to a group of chemotherapeutic agents known as dihydrofolate reductase inhibitors. It is usually given in combination with *sulfamethoxazole*, a combination called *cotrimoxazole*, and which, in infections by susceptible organisms, is superior to sulfonamide alone. Its formula is  $C_{14}H_{18}N_4O_3$ , and its CAS Number is 738-70-5.

Acyclovir is a guanosine-derived antiviral drug used to treat infections caused by chickenpox virus and shingles virus, including chickenpox, herpes stomatitis, cold sores, genital herpes and shingles. This drug works by preventing viral replication, thereby reducing the extent and duration of the disease. Its formula is  $C_8H_{11}N_5O_3$ , and its CAS Number is 59277-89-3.

Nelarabine, which is marketed under the names Arranon (US) and Atriance (EU), is a chemotherapy medication used for the treatment of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma. It is a prodrug of arabinosylguanine nucleotide triphosphate, a type of purine nucleoside analog, which causes inhibition of DNA synthesis and cytotoxicity. Pre-clinical studies suggest that T-cells are particularly sensitive to nelarabine. In October 2005, it was approved by the FDA for acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma that has not responded to or has relapsed following treatment with at least two chemotherapy regimens. It was later approved in the European Union in October 2005. Its formula is  $C_{11}H_{15}N_5O_5$ , and its CAS Number is 121032-29-9.

Propranolol is a beta blocker drug used mainly in the treatment of hypertension. It was the first effective beta-blocker produced and the only active ingredient with proven efficacy for the prophylaxis of migraines in children. It is available in generic form, as well

as in various commercial presentations. It can be used to reduce physical manifestations of anxiety such as tremors, tachycardia, palpitations, sweating, etc., typical of stage fright and performance anxiety. For this reason, it is a prohibited substance in the Olympic Games and persecuted as a sports dopant. Its formula is  $C_{16}H_{21}NO_2$ , and its CAS Number is 525-66-6.

Cimetidine was the first drug used in the cure of duodenal ulcer or stomach ulcer. Its appearance meant a revolution in the world of pharmacology, since the antacids existing until then only worked as a neutralizer, reducing the acidity in the patient's stomach. The other existing option was surgery. For this reason, the number of vagotomies (dissection of the "vagus" nerves of the stomach), which eliminated acid production, was significantly reduced. The other operation was an antrectomy, in which a piece of the stomach was cut out. Its formula is  $C_{10}H_{16}N_6S$ , and its CAS Number is 51481-61-9.

Zidovudine, Azidothymidine or AZT was the first antiretroviral drug (ARV), approved in 1987 as a drug indicated for people with HIV infection due to its effect in suppressing viral replication, although it does not represent a cure and does not guarantee a decrease in HIV infection or in the number of illnesses related to virus infection. Zidovudine reduces the transmission of HIV to other people. It is marketed under the names Retrovir and Retrovis and is an ingredient in Combivir, Epzicom and Trizivir. It is an analog of thymidine. Its formula is  $C_{10}H_{13}N_5O_4$ , and its CAS Number is 30516-87-1.

## References

1. Belle Elion, G. *Autobiography of Elion*; Nobel Prize Organization: Stockholm, Sweden, 1988.
2. Bernardo, Á. La Mujer Que Ganó un Nobel sin Tener el Doctorado. 2015. Available online: <https://hipertextual.com/2015/03/gertrude-b-elion> (accessed on 25 April 2022).
3. García García, L. Gertrude Belle Elion, Premio Nobel en Medicina. *Vidas Científicas. Mujeres con Ciencia*. 2014. Available online: <https://mujeresconciencia.com/2014/09/15/gertrude-belle-elion-premio-nobel-en-medicina/> (accessed on 25 April 2022).
4. Wayne, T.K. *American Women of Science Since 1900. Essays A–H*; ABC-CLIO: Santa Barbara, CA, USA, 2011; Volume 1.
5. Ruiza, M.; Fernández, T.; Tamaro, E. Biografía de Gertrude Belle Elion. In *Biografías y Vidas. La Enciclopedia Biográfica en Línea*; Barcelona, Spain. 2004. Available online: <https://www.biografiasyvidas.com/biografia/e/elion.htm> (accessed on 25 April 2022).
6. Más que Ciencia. Gertrude B. Elion: La Némesis de la Leucemia. 2011. Available online: <https://mqciencia.wordpress.com/2011/10/14/gertrude-b-elion-la-nemesis-de-la-leucemia/> (accessed on 25 April 2022).
7. Science History Institute. George Hitchings and Gertrude Elion. 2017. Available online: <https://www.sciencehistory.org/historical-profile/george-hitchings-and-gertrude-elion> (accessed on 25 April 2022).
8. Web Image 5. Available online: [https://es.wikipedia.org/wiki/Gertrude\\_Belle\\_Elion](https://es.wikipedia.org/wiki/Gertrude_Belle_Elion) (accessed on 25 April 2022).
9. Bailey, M.J. *American Women in Science: 1950 to the Present: A Biographical Dictionary*; ABC-CLIO: Santa Barbara, CA, USA, 2011.
10. Web Image 6. Available online: [https://en.wikipedia.org/wiki/Gertrude\\_B.\\_Elion](https://en.wikipedia.org/wiki/Gertrude_B._Elion) (accessed on 25 April 2022).
11. Web Image 7. Available online: <https://www.fisicanet.com.ar/biografias/nobelmedicina/biografias-medicina-2/hitchings-george-herbert.php> (accessed on 25 April 2022).
12. Web Image 8. Available online: <https://www.mediatheque.lindau-nobel.org/laureates/hitchings> (accessed on 25 April 2022).
13. Larsen, K. Gertrude Elion. Shalvi/Hyman Encyclopedia of Jewish Women. Jewish Women's Archive. 1999. Available online: <https://jwa.org/encyclopedia/article/elion-gertrude-belle> (accessed on 25 April 2022).
14. Web Image 11. Available online: <https://quimicafacil.net/infografias/mujeres-quimica/gertrude-b-elion/> (accessed on 25 April 2022).
15. Nobelprize.org. The Nobel Prize in Physiology or Medicine 1988: Sir James W. Black, Gertrude B. Elion, George H. Hitchings. Sweden, 1988. Available online: <https://www.nobelprize.org/prizes/medicine/1988/summary/> (accessed on 25 April 2022).
16. Colvin, M. Gertrude Belle Elion (1918–1999). *Science* **1999**, *284*, 1480. [CrossRef] [PubMed]
17. Huber, B.; Kent, R. Obituary: Gertrude Belle Elion (1918–99). *Nature* **1999**, *398*, 380.
18. Altman, L.K. *Gertrude Elion, Drug Developer, Dies at 81*; The New York Times: New York, NY, USA, 1999.
19. Avery, M.E. *Gertrude B. Elion Autobiography*; National Academy of Sciences: Washington, DC, USA, 2000.
20. Koenig, R. The Legacy of Great Science: The Work of Nobel Laureate Gertrude Elion Lives On. *Oncologist* **2006**, *11*, 961–965. [CrossRef] [PubMed]
21. MacBain, J. *Gertrude Elion: Nobel Prize Winner in Physiology and Medicine*, 1st ed.; Rosen Pub. Group: New York, NY, USA, 2004.
22. Frases333.com. Available online: <https://www.frases333.com/frases-de-gertrude-b-elion/> (accessed on 25 April 2022).