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Gertrude Elion (1918 – 1999)

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"Dear Ms Elion,

This morning I opened the news paper and I learned, with tears in my eyes, that a great honour has befallen you, the Nobel Prize in Medicine. September last year, my daughter Tiffany got herpes encephalitis. The neurologist told me that her only hope was the drug Acyclovir. You have discovered that drug. I have thanked our God, the Lord, numerous times for blessing you with the power, the love and the patience necessary to search for new medicines, all those long days, months and years. Tiffany is now in final grade and she is doing great. May the Lord bless you beyond your wildest dreams."

- Tiffany's mother

Whoever receives a letter like that – and Gertrude Elion received many – must have been an exceptionally happy woman. And she was; not just because Tiffany was cured, and her mother overjoyed. Also because she realised that she was blessed with the talent to develop lifesaving drugs with her chemical knowledge. To Gertrude, such a letter was much more valuable, and her happiness much more intense, than the scientific satisfaction that she would eventually receive: the Nobel Prize. She described it as follows: "The thrill of seeing people gets well, who might otherwise have died of disease... cannot be described in words."

Fig. 2. — Gertrude Ellion: College graduate at age 19

Difficult beginnings

As a daughter of Lithuanian migrants, Gertrude Elion was born in New York on the 23rd of January, 1918. Her father was a dentist who wanted to give his daughter a proper education. He subscribed her in Hunter College, the female division of the City College in New York. The stock market crash of 1929 hit a big hole in his pocket, but fortunately subscription was still free those days. If, as today, it had been very expensive, Gertrude probably would never have gone to college. Never would have studied chemistry. Never would have done experimental research and never would have discovered the medicines that so many people now are grateful for. The choice for chemistry was made when her grandfather was on his death bed. He lay there, at death's door, with metastasized stomach cancer, continuously moaning under the most excruciating pains. His eventual death was her turning point; against this horrible cancer, and against cancer in general, she wanted to do something. Invent something. With this motivation, she graduated with Magna cum Laude in 1937 from City College NY. With this beautiful curriculum, she wrote fifteen colleges, asking to take up a PhD. None would offer her a place. She was willing to study wherever in the United States, but without success. After another rejection, she decided to lower the bar and applied for the position of a lab technician in a chemistry lab. But even there, she missed out. It seemed like something was wrong with her! And indeed, one of her interviewers expressed it like this: "You're qualified, Miss Elion, but we've never had a woman in the laboratory before, and we think you'd be a distracting influence." Gertrude Elion didn't know what she was hearing. What do you mean "distracting influence"? Would she, just because she was a woman, never be hired, because she might distract the men? Seduce them? This was absolutely ridiculous! However, she wasn't naive. Chemistry was still a men's world, and destined to stay that way for quite a while longer. Men with a less brilliant curriculum than hers found jobs easily. She didn't. It was the sheerest sexism. But on the other hand, she was also flattered that she might be considered "distracting". As a natural redhead, she certainly wasn't unattractive, and she took great care of her clothing and appearance. Recently, an Economy student, Leonard Canter, had fallen in love with her. Apart from drawing matrixes and graphs, he could also write a decent love letter. In one of those, he called her "a brilliant woman... a vital, fresh, spontaneous and sparkling spirit... the loveliness in my life." Gertrude's answers a less romantic, however. She didn't write about butterflies. She talked about her failures and the numerous rejections on the labour market. "Don't know what will happen this winter. No money. Worried. Business school? Volunteer work? Salesgirl? Courses at Hunter or Columbia?" Out of sheer desperation, she would have accepted any job.

Smothered love

Leonard tried to pep her up with his love letters, a romantic night out, a ticket for the opera. But also

Fig. 3. — George Hitchings

Fig. 4. — George Hitchings and Gertrude Ellion 1948

with shared sorrow; although he had graduated with Summa cum Laude and felicitations, he didn't find a job right away either. To make matters worse, he was diagnosed with a cardiac disorder during a routine medical examination. "You mustn't love me, Gertie" he wrote in despair, "I'm not a full man." Another blow for Gertrude. But it became a second turning point. In her next letter, she even showed her romantic side. She wrote that she had found a recipe against her hay fever: "One large dose of L.C. (Leonard Cantor), taken as frequently as possible during the day." That would give her sufficient strength to face all misfortunes. But Leonard's cardiac condition didn't end well. Streptococcal infections on his valves (*endocarditis lenta*) took the upper hand. After the funeral, Gertrude gathered all her courage, and plunged into the first job she could get her hands on. She taught chemistry and biochemistry for three months at the nurse's school in New York. She worked half time as a receptionist at a physician's practice. For a year and a half, she worked in a chemical laboratory, where she barely made a few dollars. She managed to save some money, however, to continue her studies at the University of New York. In 1941, she graduated with a Master of Science in chemistry, with the highest distinction. When World War II erupted, many men disappeared from the labour market. This was her opportunity to finally obtain a spot in the labour market, she thought. But the only thing offered to her, was a job a supermarket's Food Laboratory. She became Quality Control Supervisor there. An impressive title, but in practice this Quality Control came down to testing pickles on acidity levels, fruit on fungal infections and mayonnaise on the right colour. After this culinary interlude, she applied to Johnson & Johnson and was offered a job working on sulphonamides. Conducting research on these antibiotics, at least she was already a bit closer to her goals, but unfortunately the department was closed six months later. Meanwhile, Elion was 26 years old and felt that she hadn't accomplished anything yet. She was still unable to participate in the fight against her father's cancer, or the fatal heart condition of her lamented Leonard.

Welcome

One day, Gertrude applied to the Burroughs Wellcome Company (now GlaxoSmithKline), where she was more than welcome. She had the good fortune of having been interviewed by the Head of Department of Experimental Therapy, George Hitchings. He quickly recognized her sparkling intellect and spirited work ethics. Amazed by both her appearance and her brilliant curriculum, he hired her. At first, Gertrude thought this would be another interim job, but she would end up never leaving this pharmaceutical company. Burroughs Wellcome, in those days, did experimental research into new medicines against infections and cancer. Precisely what she had been looking for! On top of that, her new boss was more than just a charming gentleman. George Hitchings was a biochemist

who thoroughly mastered his profession and was far ahead of his time. Even before the discovery of the DNA structure – Watson and Crick would only describe this ten years later – he knew enough about DNA to experiment with it. A colleague of his, Oswald Avery from the Rockefeller Institute in New York, had recently informed him that DNA was in fact the carrier of our genetic material. He also knew DNA was built from – amongst others – purine bases. If one were to chemically alter these purines, he reasoned, to form some kind of damaged purines (which would disrupt the synthesis of DNA), then wouldn't one have a powerful tool in hands to tackle quickly dividing cells, such as cancer cells? To even destroy them?

Rational drug design

This reasoning turned out to be brilliant. It went diametrically against the trial-and-error principle, used by former scientists looking for new drugs. At random, they would test thousands of chemicals and plant extracts, until one by chance appeared

Fig. 7. — Elion's Lab notebook

Fig. 5. — Elion in the laboratory

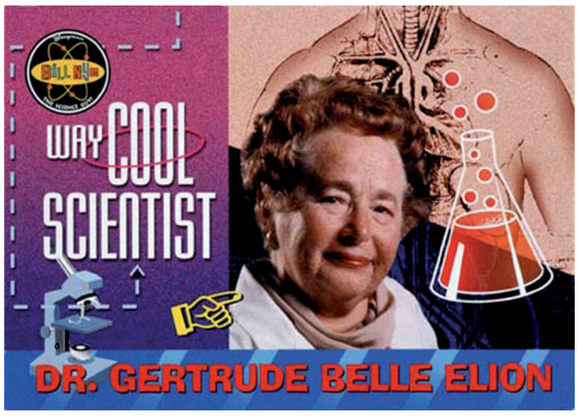

Fig. 6. — Gertrude Elion featured as a Way Cool Scientist Courtesy of GlaxoSmithKline Inc. Heritage Center

to be effective. With his approach, Hitchings went straight to the core of the case, to life's weak spot, DNA. With the incorporation of damaged purines, he aimed to decimate cell growth, as once the Greeks had defeated the Trojans by use of a fake horse. Gertrude loved the idea. Actually, she had never even heard of purines, but because of her enthusiasm, Hitchings gave her *carte blanche* to fabricate alternative purines. Normal purines are molecules with a ring of carbon and nitrogen atoms, with a few protrusions, such as an oxygen atom or an NH2-group. Applying ingenious chemical tricks, Gertrude changed some of these protrusions to other atoms. Her first trial, 2.6 diaminopurine, was a failure – way too toxic. No animal survived the tests. The next synthetic purine was less toxic but quite unstable, and it smelled like garlic. In 1951, she replaced one of the oxygen protrusions by a sulphur atom, and this proved to be a hit. She called it "6-mercaptopurine", and this 6-MP did what it was supposed to do. In a Petri dish, and more importantly in tests on animals, it disrupted cell growth considerably. Especially the most quickly dividing cells, cancer cells, suffered a severe blow. Shortly after she published her article, 6-MP was tried on one of the most fatal cancers in children, acute lymphatic leukaemia (ALL). The results were spectacular. The leukaemia cells in blood and bone marrow died off massively. The leukaemia patients improved visibly; it was as if this remarkable 6-MP had saved them from death. Unfortunately,

the effect wasn't always lasting. After a couple of months, the disease usually returned. Nevertheless, the scientific world couldn't deny this first active chemotherapeutical. Gertrude Elion and George Hitchings had certainly discovered a path worth exploring further. With a bit of well-considered chemical crafting, it seemed possible to outsmart cancer. This scientific approach, to develop new medication based on the knowledge of cell growth and purine metabolism, became known as "rational drug design".

More purine derivatives

Motivated by this success, Gertrude continued to do research and developed a number of other drugs based on these purine analogues, like azathioprine (Imuran). This wasn't an anti-cancer drug, but it turned out to be particularly effective in suppressing immunological defence. Azathioprine was subsequently used to prevent organ rejection in transplant patients, rheumatoid arthritis, Crohn's disease, myasthenia gravis and a myriad of other auto-immune disorders. Another purine analogue was allopurinol, inhibiting the production of uric acid and working wonders on gout and kidney stones. When George Hitchings retired in 1967, Gertrude Elion became Head of Department of Experimental Therapy at Burroughs Wellcome. She was the first woman ever to be put in charge of such an important research lab. Building on the concept of rational drug design, she discovered many more medicines. Acyclovir for example was a powerful agent against Herpes, the virus which had nearly killed little Tiffany. Gertrude called it her "crown jewel" and it earned Burroughs Wellcome thousands of dollars. In 1983, Gertrude officially retired, but unofficially she kept on working as an Emerita Scientist. One year later her team developed azidothymidine (AZT), the first ever drug against AIDS.

Nobel Prize

For the development of so many new medicines, and especially for the new scientific method applied to discover them, Gertrude Elion and George Hitchings received the Nobel Prize in 1988. Between all those professors in their black robes, she made a sparkling appearance as the only woman, wearing a beautiful blue evening gown. To almost any scientist, the Nobel Prize is the highest of recognitions. To Gertrude Elion, it was, in her own words, just "the icing on the cake". In the subsequent years, there were many more cakes to follow. Too many to mention, but in 1991, she received the "National Medal of Science"

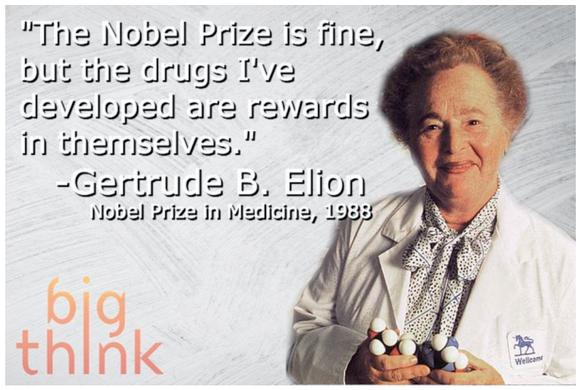

Fig. 8. — Gertrude Elion: Nobel Prize in medicine, 1988

Fig. 9. — Elion receiver the Nobel Prize from Karl XVI Gustaf, King of Sweden

Fig. 10. — Gertrude Elion receives the national Medal of Science from President George Bush

from President George Bush. The same year, she was also included in the "National Inventors Hall of Fame" for her discovery of 6-mercaptopurine. She would be the first woman ever to have the honour of appearing in this impressive row of scholars.