Obituary

Gertrude Belle Elion (1918-99)

Pioneer of drug discovery

Trudy Elion was one of only half a dozen women to receive a Nobel Prize for Physiology or Medicine this century. But although this pioneer of rational drug design was proud of her achievements, she did not care for pomp and circumstance. What she really cared about was good science, which she believed would yield effective treatments for disease. Between her retirement in 1983 and her sudden death on 21 February 1999, aged 81, she never stopped working — in fact, few people would have been aware that she had officially retired.

Elion was born in 1918 in New York, from Lithuanian and Russian parentage. Her grandfather and mother both died of cancer while she was a teenager — events that were to shape her outlook. Having earned a bachelor's degree from Hunter College in 1937, and a master's degree in chemistry from New York University in 1941, she tried to get work as a scientist. But women were rarely seen in laboratories at that time. After taking jobs teaching nurses, and testing pickles and berries for a food company, Elion finally had her opportunity when the Second World War created a shortage of labour in the pharmaceutical industry. In 1944 she got a job at Burroughs Wellcome as an assistant in the lab of George Hitchings, who was to become her fellow Nobel laureate. At the time of her retirement, she held the post of head of the Department of Experimental Therapy, a department she created. From 1983, until her death, she was scientist emeritus at Glaxo Wellcome in Research Triangle Park, North Carolina.

Together with Hitchings, Elion began by comparing normal human cells with cancer cells, protozoa, bacteria and viruses. Their aim was to pinpoint differences in how the nucleic acids are metabolized in these various cells. By exploiting those differences, the pair developed highly targeted drugs that selectively blocked the growth and replication of certain cancer cells and pathogens. This new approach to drug development was to revolutionize the management of many diseases.

In the 1940s, little was known about the synthesis of nucleic acids, beyond the fact that purines and pyrimidines are incorporated into them. To identify the pathways by which nucleic acids are built — and work out how these routes could be selectively blocked — Elion and Hitchings studied the bacterium *Lactobacillus casei*. By 1948 they had synthesized a compound which, by interfering with nucleic-acid

metabolism, inhibited growth of *L. casei*. This substance, known as diaminopurine, worked by incorporating itself into newly synthesized DNA chains in place of adenine. Although development of this molecule was eventually abandoned because of its toxic side effects, over the following three years Elion and Hitchings identified two successors — thioguanine and 6-mercaptopurine. In 1953, when 6-mercaptopurine was put into clinical trials for the treatment of childhood leukaemia, it resulted in complete remission in one in three patients.

Elion and Hitchings' approach was revolutionary. They used their understanding of the structure of nucleic acids to synthesize molecules to specific targets (rather than simply screening randomly chosen molecules, which was more common at that time). This approach yielded new drugs at an extraordinary rate. In 1950 came pyrimethamine, a drug with a strong affinity for the enzyme dihydrofolate reductase. Pyrimethamine was shown to be 2,000 times more toxic to the malaria parasite than to its human host, and as such was used successfully in the management of malaria. In 1956 an antibacterial drug, trimethoprim, arrived, closely followed by azathioprine in 1957. Allopurinol, which blocks the formation of uric acid and so overcomes gout, was discovered six years later. And in 1977 Elion's group was prominent in the discovery of acyclovir, a drug that selectively blocks the replication of herpesvirus. The Nobel committee said in 1988, when it awarded the prize, that each of the drugs was worth a prize in itself.

The success of acyclovir overturned the assumptions of many biochemists — including, at one time, even Hitchings — who believed that it would be impossible to discover effective and selective antiviral agents. Elion's persistence was key to proving these assumptions wrong. She later wrote that this change of outlook was important in preparing the pharmaceutical industry to respond to the challenge of the human immunodeficiency virus (HIV). In fact, it was researchers trained by Elion who first saw the anti-HIV potential of 3'-azido-3'-deoxythymidine (AZT), at the time an unused anti-cancer drug from the 1960s.

Under Elion, the Department of Experimental Therapy at Burroughs Wellcome grew to more than 50 people. It was a diverse group, including chemists, biochemists, virologists and oncologists, and it would prove to be a model for the future. Although

Elion never finished her doctoral work, she was awarded 25 honorary degrees and many other honours. She also served on advisory committees for bodies as diverse as the World Health Organisation and the American Cancer Society.

Even after she had formally retired, Elion's energetic figure was regularly seen walking through the labs, listening to and talking with her colleagues. But she was always a few steps ahead of their thinking on new data, gently challenging their ideas and trying to ensure that there was good rationale for their science. She was often heard asking: "If we carry out these experiments, how will we use the information generated, and where will this lead us?"

Elion's innovative ways of working and thinking are as much a part of her legacy as the drugs that she discovered and the 45 patents on which her name appears. Indeed, she trained and mentored two generations of scientists; students were swept up in her passion to pursue science and medicine; and children were inspired by her infectious smile and boundless curiosity. This is Trudy Elion's real legacy, and one with which she would be very pleased.

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