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Elected ForMemRS 1995

By Mary Ellen Avery

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In the spring of 1933 Gertrude Elion graduated from high school and that summer she had to select a major subject before she could begin her freshman year at Hunter College. This posed a quandary for the future Nobel Prize recipient, as well as holder of 45 patents, 23 honorary degrees, and a long list of other honours: she had liked all her school subjects, making it difficult to select just one. 'I loved to learn everything, everything in sight and I was never satisfied that I knew everything there was to know in each of my courses.' Fatefully, that summer her grandfather, whom she loved dearly, died of cancer. 'I watched him go over a period of months in a very painful way, and it suddenly occurred to me that what I really needed to do was to become a scientist, and particularly a chemist, so that I would go out there and make a cure for cancer.' (All quotations in this memoir are from the author's taped 1997 interview with G. B. Elion.)

Become a scientist she did, and along the way she synthesized and co-developed two of the first successful drugs for the treatment of leukaemia (thioguanine and mercaptopurine), as well as azathioprine (Imuran), an agent to prevent the rejection of kidney transplants and to treat rheumatoid arthritis. Trudy (as she was called by her many friends) also played a major role in the development of allopurinol for the treatment of gout, and of acyclovir, the first selective antiviral agent that was effective against herpes virus infections.

From her first publication in 1939 to her last in 1998, Trudy was involved in the investigation of purines and purine analogues as chemotherapeutic agents. Working in collaboration with George H. Hitchings, she synthesized a large number of purines, including 6-mercaptopurine and thioguanine, and investigated their loci of action in microbiological systems. The 6-mercaptopurine (6MP) became the first purine antagonist to be useful in the treatment of acute lymphoblastic leukaemia in children. She elucidated some alterations in metabolic

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pathways that led to resistance to the purine antagonists. Her 1954 paper that quantified the synergistic effects of purine antagonists with pyrimidine and folic acid antagonists has become a classic in the field. To make the successful 6MP, Trudy replaced an oxygen atom on the purine ring with a sulphur atom. This chemical not only had anti-tumour activity in mice but it also produced remissions, without undue toxicity, in children who had acute leukaemia. The excitement about 6MP was so great that the US Food and Drug Administration approved its use late in 1953 — only 10 months after clinical trials began and seven months before all the data supporting its effectiveness were made public (National Academy of Sciences n.d.).

Gertrude Belle Elion was born in New York City on 23 January 1918. Her father emigrated from Lithuania when he was 12 years old and went on to become a dentist in the United States. Her homemaker mother arrived in the United States from Poland at the age of 14. When Trudy was seven, the family moved from a Manhattan apartment-cum-dental-office to the Bronx, where she continued her public school education. By the time she was 12, she had been promoted two years ahead of her class. After receiving her bachelor's degree in chemistry from Hunter College in 1937, Trudy realized that neither she nor her family had enough money for her to attend graduate school. She began to look for a job, and immediately ran into the proverbial brick wall. 'Nobody … took me seriously. They wondered why in the world I wanted to be a chemist when no women were doing that. The world was not waiting for me.' Secretarial school followed, and then teaching at a hospital and a high school. She finally landed a position, albeit nonpaying, with a chemist, just to keep busy in her field; during this period she decided to pursue her master-of-science degree, which she received in 1941 from New York University. During her graduate studies, she started teaching high school chemistry and physics as a 'permanent substitute' for $7.50 a day.

Her big break came when the United States entered World War II. Since there were few men around, women came to be seen as potential employees, and Trudy was hired as an analytical chemist; her job included the measurement of the acidity of pickles and the colour of mayonnaise. After a while she tired of those functions and a spell of testing the tensile strength of sutures, and sought more meaningful work. The most interesting opening was at Burroughs Wellcome, where biochemist George Hitchings (ForMemRS 1974) was trying to make antagonists to nucleic acid derivatives. Hitchings, who would later become a member of the National Academy of Sciences, 'talked about purines and pyrimidines, which I must confess I'd never even heard of up to that point, and it was really to attack a whole variety of diseases by interfering with DNA synthesis. This sounded very exciting.' She accepted the position of biochemist in 1944 and spent the next 39 years at Burroughs Wellcome, becoming head of the Department of Experimental Therapy in 1967.

Let Trudy explain how she started out making compounds and ended up eventually with the first effective drug that induced remission in childhood leukaemia.

> At the beginning … it was my job to find out how to make (compounds). So I'd go to the library, look up the old literature to see if I could figure out how to do it. … I would just go ahead and make the compounds, and then the question was, well what do we do with these compounds? How do we find out if they really do anything? [Working with a microorganism like *Lactobacillus casei*] you could throw it in a defined medium and you could tell when you added something that was a real growth antagonist, then analyze why it was an antagonist. We knew that this organism would grow and from that it could make DNA and folic acid. … You could make everything just from the amino acids, medium, and folic acid, and so on. We knew folic acid was essential, or if you could replace folic acid with a purine, it would grow. … It would make lactic acid. If the

> organisms didn't grow, we knew we had something and we might be antagonizing folic acid or it might be antagonizing the purine. So you could with that one organism really make an analysis of three different kinds. You could add purine or folic acid and reverse the antagonism. … [We] didn't know the structure of DNA, because nobody did at the time, but [we] knew what the building blocks were, and so we were starting really at the very basic portion of the DNA and saying we don't know how it gets to be DNA … but let's find out how we can deal with it. … One of the things we had in mind was to inhibit what kills cancer cells.

By 1949 Trudy had synthesized a purine that inhibited growth in mouse leukaemia, which Joseph Burchenal at Sloan Kettering Institute in New York used to treat four patients with chronic granulocytic leukaemia, two of whom went into remission. This was the forerunner of 6-mercaptopurine, which continues to be effective in treating some cancers.

Trudy never completed the requirements for a PhD degree. Shortly after starting her new job at Burroughs Wellcome, she began night courses at Brooklyn Polytechnic Institute in pursuit of a doctor's degree. After two years the institute requested that she convert to full time to prove she was serious about the degree, but she did not wish to relinquish her exciting work. 'It was exactly the kind of job I wanted, and Dr. Hitchings was kind enough to say you won't need your Ph.D. to do the work we're doing.'

In 1983 Trudy retired and assumed the status of scientist emeritus. For the next 16 years she remained active in her field as an advisor to many organizations, including the World Health Organization and the American Association for Cancer Research. As a consultant she was also able to maintain her association with her former employer, now Glaxo Wellcome, Inc., in Research Triangle Park, North Carolina. She attracted many associates who became known as a research dream team, some of whom invented azidothymidine (AZT), a mainstay drug for treatment of HIV (human immunodeficiency virus) infection.

A most rewarding activity was her mentoring each year of a third-year Duke University medical student, who would take a year off from courses and do research under her aegis.

> I think it's a very valuable thing for a doctor to learn how to do research, to learn how to approach research, something there isn't 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 spent in research is extremely valuable to them.

Nephew Jonathan Elion MD recollects the wonder of his aunt's relationships (J. Elion, e-mail message, 15 September 1999):

> She made herself available to students. While people tell me now she was an advocate to the advancement of women in science, this actually comes as news to me, as I always thought of her as advocating the advancement of ALL persons in science. She was active in the North Carolina School of Science and Math, did lots with Duke medical students, loved to have young students visit Burroughs Wellcome (and kept a stack of books about herself directed at kids to give away). When she was a visiting professor at Brown, she didn't want to meet with the VIPs and department heads, she asked to arrange for time with the students.

Trudy was awarded the Nobel Prize in physiology or medicine in 1988 for her discovery of important principles for drug treatment.

> People ask me often [whether] the Nobel Prize [was] the thing you were aiming for all your life, and I say that would be crazy. Nobody would aim for a Nobel Prize because, if you didn't get it, your whole life would be wasted. What we were aiming at was getting people well, and the satisfaction of that is much greater than any prize you can get.

The prize was shared with her long-time associate George H. Hitchings and English scientist James Black. Others who contributed to the evaluation of her drugs included Joseph H. Burchenal of Sloan-Kettering Institute in New York and Roy (now Sir Roy) Calne (FRS 1974), a Cambridge surgeon who came to Boston to join Joseph Murray of Harvard in the hope of finding the answer to rejection of transplanted kidneys in dogs. Dr Robert Schwartz and William Damashek of Tufts University, also in Boston, pioneered the use of 6-mercaptopurine in patients. In 1998 Joseph Murray and E. Donnall Thomas of Seattle received a Nobel Prize for furthering studies of immunosuppression with azathioprine and later cyclosporin in the 1960s and 1970s. Trudy remained active in research and professional organizations and held adjunct professorships at Duke University, the University of North Carolina and Ohio State University.

Among her awards, in addition to the 1988 Nobel Prize, were the National Medal of Science, presented by President George Bush in 1991; the Garvan Medal from the American Chemical Society in 1968; the President's Medal from Hunter College in 1970; the Judd Award from Memorial–Sloan Kettering Institute in 1983; the Cain Award from the American Association for Cancer Research in 1984; the Ernst W. Bertner Memorial Award from the M. D. Anderson Cancer Center; the Medal of Honor from the American Cancer Society in 1990; and 23 honorary degrees. She was elected to membership in the National Academy of Sciences in 1990 (and served on the Council) and to the Institute of Medicine in 1991. She was a fellow of the American Academy of Pharmaceutical Scientists and the American Academy of Arts and Sciences; a Foreign Member of the Royal Society; and an honorary member of the Spanish Academy of Dermatology and Venereology, among many others.

Trudy's favourite pastimes were photography, music (especially Puccini, Verdi and Mozart operas), travel ('I'll climb a mountain to get a picture,' she said in 1993 during an interview with the *Tampa Tribune*), and a passion for raspberries.

> Over the years, my work became both my vocation and avocation. Since I enjoyed it so much, I never felt a great need to go outside for relaxation. Nevertheless, I became an avid photographer and traveler. Possibly my love for travel stems from the early years when my family seldom went away on vacation. Thus, my curiosity about the rest of the world did not begin to be satisfied until I began to travel. I have traveled fairly widely over the world, but there still remain many places for me to explore. Another major interest is music, not because I am musically talented, but because I love to listen to it. I am an opera lover and have been a subscriber to the Metropolitan Opera for over 40 years. I also enjoy concerts, ballet, and theatre. (*Les Prix Nobel* (1999).)

Jon Elion remembers vividly one particular scene from the Nobel festivities in Stockholm:

> The ceremonies are held in an ornate and regal hall. The laureates and other officials are seated on the stage, all men except for Trudy. They are all dressed in black and white, all very staid, stiff, and proper. Trudy stands out … in her 'Trudy blue' chiffon dress. She is relaxed and is enjoying every minute. She was a lifelong opera fan. … The chamber orchestra strikes up one of the arias from Mozart's *Don Giovanni*. Trudy smiles, as if they were playing this just for her. She taps her foot and nods her head in time to the music, no doubt thinking of the words to the aria as the music is played. This was in such stark contrast, as the men continue to sit black-and-white and stiff, while 'Trudy Blue' Dr. Elion smiles, nods, taps, and mentally sings.

In Jon Elion's words again (J. Elion, e-mail message, 15 September 1999):

> The day after she died, I was sorting through her mail. There were two letters that struck me as representative. One was from a university president thanking her for being a visiting professor

> there. The other was from a young girl. … The girl talked excitedly about a school project in which they were doing a wax museum, and the students would play the wax figures. She had researched scientists on the Internet and had selected Trudy as her heroine. Her mother subsequently sent me photos of the girl dressed in a lab coat, holding a beaker, and with an imitation Nobel medal around her neck. I know that Trudy would have nodded briefly while reading the letter from the university president, but would have read and reread the letter from the young girl, and would have taken the time to respond. I did that for her, and sent the girl Trudy's last copy of the book she liked to give out.

The following is from her handwritten notes for a lecture to students (J. Elion, e-mail message, 15 September 1999):

> It seems like only yesterday that I was sitting where you are now. Time passes rapidly when you are having fun. Have a goal that you really care about (cancer research). 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. It's true it took seven years of various jobs, including a year in graduate school and two years of high school teaching before the shortage of men in civilian jobs gave me the opportunity to prove myself. But after that, I never looked back.
>
> It is important to go into work you would like to do. Then it doesn't seem like work. You sometimes feel it's almost too good to be true that someone will pay you for enjoying yourself. I've been very fortunate that my work led to useful drugs for a variety of serious illnesses. The thrill of seeing people get well who might otherwise have died of diseases like leukemia, kidney failure, and herpes virus encephalitis cannot be described in words. The Nobel Prize was only the icing on the cake. There may be those who try to deter you and discourage you along the way. But keep your eye on the goal. And in the words of Admiral Farragut, 'Damn the torpedoes, full speed ahead!'

I recall Trudy saying, 'I don't really want to die until I'm used up.' On Sunday, 21 February 1999, she went for her daily walk, but never made it home. Trudy collapsed and was taken to the University of North Carolina Hospital in Chapel Hill, where she died at midnight at age 81. She was never used up.

She is survived by four nephews and two nieces, to whom she was devoted. She is greatly admired by a host of students and colleagues who remember her brilliance, devotion to science, and drive to find a cure for cancer. Little did she anticipate the myriad drugs that she would synthesize for so many diseases, including some forms of malignancies. This great humanitarian rejoiced when she could be helpful to others, and her enthusiasm for her work was contagious.

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