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## **Nucleosides, Nucleotides and Nucleic Acids**

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### **In Memoriam: Dr. Hermione Anne Simmonds**

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**Dr. Hermione Anne Simmonds**  
**(December 6, 1927 –April 2, 2010)**

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Although Anne was not able to attend the international symposium commemorated in this volume, she was a solid supporter of the international series. Anne took part in every meeting on Purine and Pyrimidine Metabolism in Man from the first one—held in June 1973 in Tel Aviv, Israel, and organized by Oded Sperling, until she became too infirm for international travel some five years ago. Her group from the Purine Lab at Guys Hospital were usually among the biggest contributors to the meetings, and Anne's oral presentations, chairing of sessions, poignant questioning, and insistence that everyone had a good time will be remembered by all who attended over the years.

Anne (she never used her first name, although she frequently used her initials, HAS) was born in 1927 on a remote farmstead near Kohu Kohu, North Auckland, New Zealand. She was the middle of three sisters of English stock. Her sole primary education was via correspondence school, but she went on to attend the Girls' High School in Whangarei, New Zealand's

most northerly city. Anne graduated from a local college with a M.Sc. in organic chemistry on May 6, 1949. Deciding to put her degree to a practical use rather than study for a Ph.D., she entered the local hospital, and, by February 1952, she had gained her certificate of proficiency in the hospital laboratory practice of bacteriology. Interestingly, this was very much a subject she became scornful of, in terms of purine metabolism, in later years. During the early years in New Zealand, she gained a love of the outdoors especially walking and skiing, passions that she retained to the very end of her life.

At some time in the mid-1950s, she left New Zealand and started to travel, first to Norway then to North America with a friend, Anna Shepherd, from New Zealand. On this trip they tried to drive to the Arctic Circle in an old car, but turned back when it became too cold and then headed south to California where they gate crashed the 1960 Winter Olympics in February 1960 in Squaw Valley. In 1962, Anna and Anne took part in an archaeological trip under the direction of the maverick archaeologist, John Allegro, to investigate the Dead Sea Scrolls. They travelled to the “dig” by motor scooter from England eventually arriving in Jordan just before Christmas. Allegro’s book, *Search in the Desert*, published in August 1963, includes a number of references to and photographs of Anne in the desert and also recalls a tale she would often tell of being taken seriously ill following a bite from a camel. She was near death when they broadcast for help. King Hussain of Jordan, a radio ham, heard the message and sent a plane to pick her up and she spent a month in an Amman hospital recovering—she almost had gangrene.

The plan then was to return to New Zealand on the motor scooter; however, the scooter died in the Middle East and the pair made a circuitous journey to Malaysia, with their final leg of the journey completed by plane. Back home, Anne returned to hospital pathology work.

It was then, while working in the renal unit in Auckland, that the events that led her to move toward purine metabolism occurred. Anne recalled that in 1963 she was asked “to help Dr. David Becroft, then Head of the Princess Mary Children’s Hospital, to investigate a baby boy, half-Maori and half-Irish, who was failing to thrive, had an untreatable anaemia and was passing unidentifiable crystals. My job was to identify the crystals. This child had the rare pyrimidine disorder, hereditary orotic aciduria.” This patient is still alive and well. Following this, Anne, who was now working as a biochemist in the Medical Unit at Auckland Hospital, started to develop analytical methods for the determination of the more abundant purines, for example, uric acid, hypoxanthine, and xanthine using anion exchange fractionation followed by TLC. This work also led her toward gout and its treatment with allopurinol.

In 1966, Anne was looking to develop her new interests and decided that she would need to leave New Zealand. So, in late 1967, Anne traveled again to Europe. She started work in 1968 at the Wellcome Research Laboratories, Beckenham, South London. This famous pharmaceutical research center was often known as the “University of Beckenham” since the staff had almost

academic freedom to pursue their research interests. The company was already involved with purine and pyrimidine research through its groundbreaking work on anticancer and antiviral drugs such as 6-mercaptopurine patented in 1954 and allopurinol for the treatment of gout. For their work on these drugs and many other drugs, Gertrude Elion (1918–1999) and George Hitchings (1905–1998) received the Nobel Prize in Physiology or Medicine in 1988. Although they worked at the American half of the company, Anne got to know them and they developed a close friendship that lasted until their deaths at the end of the 1990s. Wellcome allowed Anne to register for her postponed Ph.D. via the London University scheme that permitted those in suitable establishments to be industrially based students. She gained her Ph.D. in November 1970.

It was about 1969 that I, a new and very junior research assistant in the Medical Unit at St. Bartholomew's Hospital, first met Anne when she came to visit Dr. Dickie Watts and Dr. Betty Dean, with whom she was collaborating on some purine metabolism studies using  $^{14}\text{C}$  labelled substrates. On a daily basis, she would appear with 24-hour urine collections from a gout patient and ask me to measure its pH: the urinary pH in gout being remarkably constant.

Following her graduation, she was invited by Dr. Rodney Graham and Dr. Stewart Cameron to set up the Purine Research Laboratory at Guy's Hospital adjacent to London Bridge to study purine metabolism in their patients with gout and renal failure. The unit was established around 1971, and in 1974, it moved into the newly completed 34-story Guys Tower. From the Purine Lab on the 17th floor visitors had a magnificent view over the City of London. The lab remained at Guys until 2008 when it moved to the sister hospital, St. Thomas, opposite the Houses of Parliament. For more than 20 years, the purine lab never received adequate funding and its staffing and running expenses were always hand to mouth. Nevertheless, under Anne's leadership its research output increased and it became an international center for purine and pyridine research. Visiting researchers came from across Europe and farther afield to work in the laboratory and benefit from its referred patient population.

My first article with Anne was published in 1974<sup>[1]</sup> and was concerned with the comparative availability of a new Wellcome drug, Thiopurinol. In 1976, working with my mass spectroscopy colleague at Barts, Walter Snedden, Anne described "a new cause of urinary calculi; 2,8-dihydroxyadenine," that is, APRTase deficiency.<sup>[2]</sup>

My own work on the new technique of HPLC for nucleotide measurement and later nucleoside measurement excited Anne and soon large numbers of samples kept arriving from Anne for analysis. In 1972, Eloise Giblett, who died last year, published her observation of ADA deficiency associated in two patients with SCID.<sup>[3]</sup> I particularly remember that following the publication by Mills et al. of their quantitative work on purine metabolism in

the disorder<sup>[4]</sup> Anne's immediate response was "that man is not a mouse," their interpretation of their observations must be wrong and the answer lies with deoxyadenosine metabolism.<sup>[5]</sup> Although I could easily resolve deoxynucleotides from ribonucleotides, we had to wait until 1977 for the first case of ADA in the United Kingdom. Within days, I had shown that Anne was right, but a publication from the United States announcing the same finding a few days later took the shine off our own findings.

Anne's sense of fair play and support for younger researchers began to play a major role in her professional life. The continuous need to seek funding for the purine lab, including her own salary, the lack of academic recognition, and the fact that her researchers were always on short-term contracts led her to start campaigning for better conditions for such workers in the United Kingdom. In 1978, she wrote to *The Lancet*<sup>[6]</sup> about the lack of suitable career opportunities for researchers in the United Kingdom. A string of further publications followed and she had clearly voiced a major problem in the U.K. system of funding medical research. This led to the formation of the Association of Researchers in Medical Science (ARMS) to actively campaign for better employment conditions for contract and related research staff. It eventually achieved support from the Wellcome Trust, some of the U.K. Research Councils, and some members of Parliament, but universities were never entirely happy with the campaign. Anne was a tireless campaigner for ARMS, but after some 25 years and after Anne's retirement, ARMS is now ceasing its work.

Around 1985, Anne also became somewhat disillusioned with the purine symposia series, feeling that its international focus left Europe behind and also discouraged the attendance of younger workers. For a number of years, Anne collaborated with Francoise Roch-Ramel on aspects of urate transport and they, along with others, established the European Society for the Study of Purine and Pyrimidine Metabolism in Man (ESSPPMM). The first meeting of the new society was held in Roch-Ramel's hometown of Chateau d'Oex, Switzerland, in September 1987. It fully upheld Anne's principles—being very cheap: We all stayed in an out-of-season ski lodge or tents, young researchers were welcomed to speak and present, and everyone paid—be they an international star or a first-year student. Researchers took their families and would spend the afternoons visiting the mountains and being made very welcome by the local townspeople. A second meeting was held in Bavaria, where the decision was taken to hold a joint meeting of the International Series and ESSPPMM in Bournemouth England in 1991. Anne and her committee put everything into that meeting. She managed to get the large modern conference center on the seafront for free. We raised considerable sponsorship and the meeting attracted probably the largest number of delegate for the series with over 400 attendees. We finished the meeting with a surplus, some of which was returned to charitable sponsors and the remainder was used to establish the PP91 fund, which I administer

and which continues to support attendance at purine meetings of young researchers.

As an indication of the high esteem in which Anne's colleagues held her, the next international symposium, held at Indiana University, Bloomington, Indiana, USA, in May 1994 was dedicated to her. The Purine Lab's researches continued to diversify into for example azathioprine pharmacogenetics. Anne herself continued to argue in favor of metabolism and was often scathing about the role and purpose of molecular biology. Because of its diagnostic role, which continued to grow, and following extensive lobbying by Anne, the Purine Lab began to receive, from 1990, some NHS funding. Anne, herself, never received the academic promotion her work deserved and had only been appointed to a senior lectureship by her official retirement in the mid 1990s. Retirement did not stop her being in the lab on a daily basis. She even continued her daily attendance even when the laboratory transferred to St. Thomas' in 2008.

Anne was also linked to the establishment of a charity dedicated to purine and pyrimidine disorders. The Purine Metabolic Patients' Association (PUMPA) was founded toward the end of 1992 by a small group of patients and friends to help patients and their families who suffer from any of the 28 hereditary purine or pyrimidine metabolic disorders. Anne was instrumental in PUMPA's work and PUMPA became a registered charity in March 1993. As well as supporting research into these disorders, both in the Purine Lab and elsewhere Anne arranged PUMPA's annual conference, which is a unique gathering where patients and their families meet with researchers and clinicians.

In 1998, Anne obtained a grant from the European Union to establish a network of laboratories for the diagnosis and study of disorders of purine and pyrimidine metabolism. As a result of this grant, most countries in the EU now have at least one laboratory able to diagnose purine and pyrimidine disorders.

Without any doubt, Anne was a driving force in the development of our understanding of Purine and Pyrimidine Metabolism in Man. In total, her publications ran to 428, including many book chapters, and with her last publication appearing in 2008. Her books include *Purines: Basic and Clinical Aspects*<sup>[7]</sup> and *Gout—At Your Finger Tips*.<sup>[8]</sup> If anything, her skills and memory live on with all those who visited the Purine Lab and took the skills in diagnosis and understanding that they learnt from Anne back to their own countries and their own laboratories, not forgetting the families she helped.

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