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Mollie Elizabeth Holman 1930–2010

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Mollie Holman was a biophysicist whose work on the autonomic nervous system and the innervation of smooth muscle was seminal in advancing knowledge of its behaviour at a cellular level. She was particularly known for her technical expertise in microelectrode recording of membrane potential from single smooth muscle cells, and the interpretation of their electrical activity, both spontaneous and in response to transmitters released from their autonomic nerves.

Mollie Elizabeth Holman was born in Launceston, Tasmania, on 18 June 1930 and died in Melbourne on 20 August 2010 after a long illness. Mollie was a distinguished electrophysiologist who made major contributions to our understanding of the cellular mechanisms underlying the excitation of smooth muscle and the actions of its innervation by the autonomic nervous system. Her work was seminal in the development of knowledge of the functioning of the vascular and visceral tissues of the body. She was involved in training and encouraging a whole generation of autonomic neurobiologists who have led the world in this field for many years. Most of her career was spent at Monash University in Melbourne, which she joined soon after its establishment and where she remained for the rest of her working life.

Mollie qualified for a Bachelor of Science in Physics (1951) and Master of Science in Physiology (1954) at the University of Melbourne and then went to the United Kingdom on a Melbourne University Travelling Scholarship to work on the physiology of smooth muscle at the University of Oxford. She received a DPhil from Oxford in 1957. Mollie returned to Australia in 1958 to take up a Lectureship in Physiology at the University of Melbourne. In 1963 she moved to the Department of Physiology at Monash University. Initially appointed as a Senior Lecturer, she was appointed Reader in 1965 and Professor in 1970. Mollie retired in 1996.

Early History

Mollie was the eldest of four daughters of William Prout Holman and Mollie Bain. Her father was a pioneer radiologist who set up the X-Ray Department in the hospital in Launceston. He strongly supported his girls in their academic pursuits and had a strong influence on Mollie during important times in her life. Starting her primary education in 1938, Mollie attended, until the Intermediate year, the girls' grammar school Broadland House in Launceston, where she quickly rose to the top of her class. She showed the first signs of her future interests when, at the age of 14 years, she enrolled in evening classes in a course called 'Introduction to science and engineering'. She loved these studies because 'it all seemed very logical and satisfactory'. Mollie moved to Melbourne in 1945 to complete her secondary education as a boarder at Melbourne Church of England Girls'

Grammar School (Merton Hall) where she was able to study science to prepare her for matriculation. She edited the school magazine, played basketball and developed a passion for Greek and Roman history that she kept throughout her life. Her chemistry teacher left a great impression, leading Mollie on to study science at the University of Melbourne.

University Studies

In her first year at the University of Melbourne, Mollie was based in Mildura at a spillover campus for the additional students entering the university in the immediate postwar years. While enrolled in Science, she took the subjects for the first year of the medical course plus Pure Mathematics, which gave her a strong basis for her later career. She graduated with Honours in Physics in 1951, having also studied Physiology and Biochemistry in her final year, and gained a Melbourne University scholarship for further studies. She joined the Department of Physiology and Pharmacology, then under the leadership of R. D. Wright (a friend of her father, who had by then moved to Melbourne to be head of the radiotherapy unit at the new Peter MacCallum Cancer Hospital) and studied biophysics, a very new subject at the time. Her supervisor was Frank Shaw (to become the first Professor of Pharmacology at Melbourne in 1954) who suggested that she measure the voltage generated by sodium ions pumped across frog skin—subsequently a classical model for epithelial transport [1]. The project involved building her own electrodes and recording apparatus. In 1953 and 1954, Holman was a demonstrator in Pharmacology as well as working on her research. She completed an MSc at the University of Melbourne in September1954 with a thesis entitled 'Pharmacology of Bioelectricity'. She had given her first scientific paper at an ANZAAS meeting in Canberra at the beginning of 1954.

During this time, she started to read about the autonomic nervous system. This system consists of the nerves that control all the organs and tissues of the body except skeletal muscles, a subject that fascinated her for the rest of her life.

Oxford

Since it was unusual to carry out postgraduate studies in Australia at that time, Mollie went to Oxford to study for a DPhil under the supervision of Professor Edith Bülbring in the Department of Pharmacology headed by J. H. Burn. She had been dissuaded by John Eccles (later a Nobel Laureate) from going to University College London where Bernard Katz led the Biophysics Department. Eccles had worked on smooth muscle at Oxford with Charles Sherrington and suggested that this would be a more novel area than currently fashionable studies of the skeletal neuromuscular junction.

Edith Bülbring was a formidable lady and Mollie and she did not always agree. Bülbring had had a long, successful career as a classical pharmacologist using smooth muscle tissues but had developed an interest in smooth muscle physiology. The field of smooth muscle research was in its infancy. Since smooth muscles form the major part of blood vessel walls, dysfunction leads to disorders of blood pressure and flow. Similarly the intestines, reproductive organs, bronchioles and urinary tract organs all depend upon the ordered functioning of the smooth muscles present in their walls. It was also known that the activity of smooth muscles was controlled by the electrical gradient across their cellular wall, termed their membrane potential.

At the time of Mollie's arrival in Oxford, the conventional wisdom was that membrane potentials could only be measured using sharp glass microelectrodes filled with a conducting solution. These were very fine micro-pipettes: narrow tubing was heated in a flame until it was white hot and then pulled to make a very fine capillary tip that was hopefully patent. The pipette was filled with concentrated potassium chloride as a conducting solution—if you were lucky and the tip of the electrodes did not break off when the pipettes were boiled under reduced pressure in concentrated potassium chloride solution. The sharpness of the electrode was defined by its tip diameter which, since it was too small to be viewed in the light microscope, was assessed by measuring its resistance—the finer the tip, the higher the resistance. At the time, the conventional wisdom was that any electrodes with resistances above 10 MΩ were likely to be incompletely filled and therefore unusable.

Pushing such electrodes into smooth muscle resulted in resting (trans)membrane potentials of about −10 mV (inside relative to the

external solution), with action potentials having amplitudes of some 5 to 7 mV. Action potentials are brief positive-going potentials exhibited by all excitable cells—such as nerve and muscle cells. Edith Bülbring had published several papers showing such records. Moreover, as the discharge of action potentials was suppressed by the removal of Na^+ ions, it was thought that smooth-muscle action potentials resulted from an inward movement of Na^+ ions. Mollie reasoned that given the small diameters of smooth muscle cells (2–3 μm diameter), the electrodes being used were likely to damage the cells and give unreliable measurements. She therefore developed a protocol for manufacturing electrodes with much finer tips; these had resistances of some 60 to 80 MΩ. With these, she found that the resting membrane potentials of smooth-muscle cells were, as in many other excitable cells, around −70 mV [3–5]. Further, the peak of the action potential often overshot 0 mV (that is, their amplitude was nearly 100 mV), and changing the ionic concentrations (as she had done with frog skin) indicated that the ions entering the cells were Ca^{2+}, not Na^+.

At the time, these findings were greeted with general disbelief: Mollie had overturned many of the recent findings made in the Oxford laboratory. Furthermore she had used electrodes that were thought to be unreliable. The day was carried, however, by two of Mollie's most charming attributes. First, she was modest and encouraged discussion about her possible failings. Second, rather than hoarding her new technical skills, she shared them with others, in particular her Japanese colleagues Hiroshi Kuriyama and Tadao Tomita, who rapidly validated her observations. These aspects of Mollie's character led both to rapid growth in understanding of smooth muscle electrophysiology and the generation of a fine spirit of camaraderie amongst smooth-muscle workers from all continents that persists to this day.

Mollie's success in correcting Bulbring's observations on membrane potentials and action potentials in smooth muscle was the talk of Oxford biological sciences. It also gained her considerable esteem within Britain's Physiological Society. She later became an international leader who was highly regarded in Europe and North America as well as in Britain, Australia and Japan. She did not broadcast her achievements but she was immensely respected by physiologists and clinicians alike.

While in Oxford, Mollie befriended Mike Rand, an Australian who was working with J. H. Burn and was soon to become the second Professor of Pharmacology at the University of Melbourne) and Geoffrey Burnstock (a post-doctoral fellow in Edith Bülbring's laboratory). Geoff was originally from London and was soon to become Professor of Zoology at the University of Melbourne.

Return to Melbourne

After graduating at Oxford in 1957, Mollie was offered a lectureship in R. D. Wright's Department of Physiology and went back to the University of Melbourne where she set up her own laboratory in the departmental paint store. She started experiments, initially using equipment borrowed from David Dewhurst until she obtained grant funding for newer recording apparatus. She developed her collaboration with Geoff Burnstock to work on the electrophysiology of neuromuscular transmission in the guinea-pig vas deferens. At that time it was widely held that the autonomic nervous system lacked sophistication: the sympathetic nervous system was thought to be switched on in much the same way as one would turn on a tap. By recording the membrane potential of the smooth muscle cells during electrical stimulation of the sympathetic postganglionic nerves, Mollie identified excitatory junction potentials (ejp's) that she showed were analagous to the endplate potentials recorded at the neuromuscular junction and excitatory postsynaptic potentials in the central nervous system [6, 7]. Mollie's studies on the vas deferens revealed that the nerves released quanta of transmitter [9] and the effects of these summed to give rise to post-junctional excitatory potentials in the smooth muscle cells. If sufficient synaptic activity occurred, the potentials summed to trigger action potentials, whilst low-level activity demonstrated patterns of facilitation detected elsewhere [16]. Once again the conventional thinking had been overturned and great progress made. Mollie and Geoff Burnstock published a series of pioneering papers describing this work [6–11, 13, 14, 16, 17].

A major puzzle was that the responses to sympathetic nerve stimulation were not blocked by

adrenoceptor antagonists [17], which was surprising since noradrenaline was well established as the neurotransmitter released by sympathetic nerves, and adrenoceptor antagonists block most of the contractile responses. It was not until over twenty years later that Burnstock and several other groups showed that the ejp's were the membrane's potential change in response to adenosine trisphosphate (ATP) released as a co-transmitter with noradrenaline from sympathetic nerves.

During this time, Mollie and Geoff collaborated with Graeme Campbell and Max Bennett, then postgraduate students of Burnstock, to discover the non-adrenergic, non-cholinergic (NANC) inhibitory innervation of the guinea-pig taenia coli [12, 15]. Later Mollie came to accept that ATP is involved as a co-transmitter in this and other autonomic systems, although she (and many others) resisted this idea for years [51] until a large range of purine receptors was identified by Burnstock and others.

Research at Monash

In 1963 Mollie moved to the Department of Physiology at Monash University, enticed by Archie McIntyre, FAA, the foundation professor and a major driving force behind Australia's excellence in neurophysiological research. Initially appointed as a Senior Lecturer, Mollie was appointed Reader in 1965 and to a personal chair in Physiology in 1970. Much of Monash's international reputation in biological and medical science in the 1970s and 1980s was due to her scientific accomplishments. In 1965, she was awarded the Edgeworth David Medal by the Royal Society of New South Wales for her achievements as a scientist aged under 35, and in 1970 Monash awarded her a Doctor of Science degree.

Mollie collaborated with Gary Blackman at the University of Otago in New Zealand to use microelectrodes to study the synapses in autonomic ganglia [31]. They extended and improved the first recordings made by others by using finer-tipped electrodes and applied these in intact preparations of ganglia and smooth muscles. At her initiation, studies were begun on ganglia exerting control over gastrointestinal motility [34, 35]. These studies led to the first unequivocal demonstration of a peripheral reflex between intestinal afferents and sympathetic projections to the colon that did not involve the spinal cord. Other studies led to an understanding of the properties of myenteric neurons in the enteric ganglia and, for example, the prolonged afterhyperpolarizations that limit the firing properties of these and many other types of neuron, including in the central nervous system [38, 39] (Fig. 1).

Figure 1. Mollie Holman at the dissecting microscope preparing smooth muscle tissue for electrophysiological recording *in vitro*, in the Department of Physiology at Monash University in 1978 (image by Herve Alleaume, courtesy of Monash University Archives IN268).

At Monash in the 1970s and into the 1980s, Mollie established and led the Neuropharmacology Group, which included Robert Bywater, David Hirst, Elspeth McLachlan and Grahame Taylor. The Group was rather special, being composed of academics who were all more or less interested in the same things, namely smooth muscle and other targets of the autonomic nervous system and the nerve pathways themselves. It was a rather unusual situation to have so many individual academics with overlapping interests and with the ability to be independent at the same time as being part of the group. It was not at all like the modern groups working under a senior scientist. Mollie gave everyone encouragement to work on what they wanted and she supported us all. We met weekly to discuss our results and problems that we needed help to solve.

Often, someone would come up with a completely different approach—sometimes a technical idea, sometimes an intellectual solution. And Mollie was present as a group leader, much like a cheerleader providing drive and inspiration but not directing, to help us achieve our goals. She pointed us to relevant literature and passed on the latest developments she had heard about at meetings overseas.

There were many notable international visitors to the Group at that period: Ladd Prosser [11], Ed Daniel [43], Joe Szurszewski [33, 34] and Gerry Silverberg from the USA, Hiroshi Kuriyama [16], Tadao Tomita [41] and Y. Hashimoto [23, 26, 27] from Japan, Tom Muir [33] and Hugh McKirdy [39] from Glasgow, Donald Cheung from Canada, Nick Spitzer and Alan North from the USA, and Wilfrid Jänig from Germany. There were also many students and postdoctoral fellows, including Annmarie Surprenant [45, 47, 48, 50, 52], Tim Neild [46, 50, 52], Rick Lang [53], Helena Parkington, Harry Coleman and Mary Tonta [55–58], Terry Smith, Susan Luff and Marianne Tare, some of whom later joined the academic staff at Monash or other universities internationally. A symposium held in Mollie's honour in 1992 at Great Keppel Island, Queensland, was attended by most of her Australian and international colleagues.

From the late 1980s, Mollie was less involved in the laboratory although she continued to play the same supportive role for the members of the Group. In the 1990s she did some interesting experiments with Parkington and Coleman, recording from cells in the adrenal medulla that had many of the properties of neurons in sympathetic ganglia [55, 56, 58]. Later, her interest in the control of the gastrointestinal tract by the enteric ganglia led to her involvement in studies of the inhibitory regulation of the mouse colon with Nick Spencer, a student with Bywater and Taylor [59, 60]. A dinner attended by many of Mollie's past colleagues was held in Melbourne in 2007 to celebrate the fiftieth anniversary of her first publication in the *Journal of Physiology*. The dinner was organized by Alan North, by then at the University of Manchester and President of the Physiological Society.

During Mollie's years at Monash, Archie McIntyre, FAA, and then Bob Porter FAA, were Heads of Physiology and they and Mollie led the most exciting and productive department of physiology in Australia at that time.

Outside the Laboratory

Mollie was active as a member of the Australian Physiological Society, presenting many papers at its meetings and serving terms as National Secretary and later as President (when it was the Australian Physiological and Pharmacological Society). She led the editorial committee that put together the first volume of the *Proceedings* of the Society, published in 1970, and was elected to Honorary Membership after her retirement.

Mollie was also involved in significant roles within the Australian and New Zealand Association for the Advancement of Science (ANZAAS), served on the Victorian Board of the National Heart Foundation (1975–7) and took on major responsibilities with research organizations like the Australian Research Grants Committee, forerunner of today's Australian Research Council. She was the first female member of the Executive of the Commonwealth Scientific and Industrial Organisation (1975–7). In all these activities she was never the token female—she fully embraced her responsibilities and worked tirelessly in the promotion of the highest levels of scientific integrity.

In 1985, Mollie was awarded the ANZAAS Medal, for services in the advancement of science or administration and organization of scientific activities, or the teaching of science throughout Australia and New Zealand and in contributions to science that lie beyond normal professional activities. The medal was presented by Sir Edmund Hillary (Fig. 2).

Mollie was elected a Fellow of the Australian Academy of Science in 1970 and served on several of the Academy's committees including the Biophysics and Pharmacology Group (1968–82, Chair 1973 and 1979), and what was then numbered Sectional Committee 6, the sectional committee covering her field of science (1972–6, including Chair 1974–5; 1984–7, including Chair 1985–7). She also served on the Academy's Council (1980–3) and was Vice-President (Biological Sciences) in 1982–3.

Within the Physiology Department at Monash, Mollie's involvement in teaching was focused for many years on running the Honours course, for

Figure 2. Sir Edmund Hillary presenting Mollie Holman with the ANZAAS Medal in 1985 (cropped from original image, courtesy of Monash University Archives IN1321).

which she used her experiences at Oxford as a model. She was a strong mentor to all Physiology graduate students over the course of her career. She later spent a great deal of her time in research administration, including a period as Associate Dean of Research of the Faculty of Medicine. She retired from Monash in 1996. Mollie was awarded an Honorary Doctor of Laws degree by Monash in 1999. In 2007 she received the David de Kretser Award for her exceptional contribution to the University (Fig. 3).

Mollie's great strength, aside from her excellence as a scientist, was her ability to support and encourage others. With each visitor, Mollie provided amazing support. With each new staff member, whatever their field of study, Mollie ensured that their research efforts could proceed without interference. Most notably, she supported young scientists. She would seek them out and aid them in their studies. At scientific meetings, both in Australia and overseas, she would invariably be seen encouraging younger workers, promoting their efforts. Her contributions in this way were recognized by Monash by the creation of the Mollie Holman Medals, awarded each year to the best PhD thesis in each Faculty.

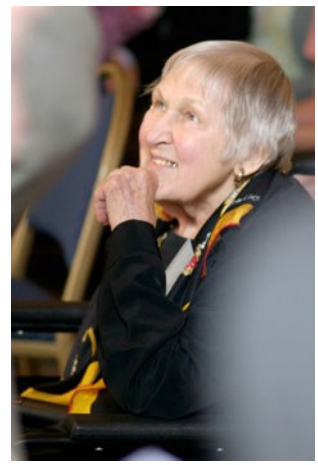

Figure 3. Mollie Holman in 2007 on the occasion when she received the David de Kretser Award for her exceptional contribution to Monash University (image from *Monash University News*).

Mollie was appointed an Officer of the Order of Australia (AO) in 1998.

Life beyond Science

Mollie had many interests outside her science and the academic life. She was a hiker, an accomplished skier and an intrepid traveller, particularly in India and the Middle East, with many stories to tell on her return to Melbourne. She also loved Greek and Roman history and did trips to several archaeological sites. As well, she enjoyed painting in watercolour.

Mollie suffered a couple of strokes in the 1990s from which she determinedly recovered. After one of these, she started driving again after the minimum three months, much to the dismay of some of us as she was only just beginning to walk without a stick. She continued her interests in travel and history and was always keen to hear the scientific gossip when any of her old colleagues visited her.

Just a few weeks before Mollie died, she was mentally as bright and interested as ever and insisted on winning her hand of Scrabble before she would chat with visitors. It was a shock to hear that she died so soon afterwards. Mollie was a peerless scientist and her lasting memory is one of generosity of spirit, her support for the young and her sense of a fair go for all. She leaves a great scientific legacy and many friends and colleagues who still treasure her input to Physiology.

Acknowledgements

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