In Memoriam for *Journal of Physiology*

Thomas (Tom) B. Bolton - a major force in smooth muscle research

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Tom was born on 14 November 1941 to Tom and Winnie (née Halstead) in Sunderland, England. His father was killed in July 1941 when his plane was shot down over the North Sea. Winnie and Tom settled in Yeadon, West Yorkshire and Tom was educated at Woodhouse Grove School in Bradford. He obtained a First Class Honours Batchelor of Science degree in Physiology at the University of London in 1964 and a PhD in Pharmacology in 1967, which he passed after examination by the eminent pharmacologist Sir John Vane. He subsequently completed a Bachelor of Veterinary Medicine and was admitted to the Royal College of Veterinary Surgeons as a practising veterinary surgeon. He remained active as a vet and was for many years the vet responsible for the animal facility at St. George's Hospital Medical School (now St. George's University of London), which was where he dedicated most of his working life to teaching, research and university leadership.

Tom first became interested in research and particularly smooth muscle research through his time at the Department of Pharmacology Oxford University where he was a Royal Society Locke Research Fellow at Brasenose College. He was greatly inspired by the late Edith Bülbring who lived until 1990 and is widely regarded as the mother of smooth muscle physiology. In 1976, Tom became Senior Lecturer at St. George's. Within 4 years he was professor and 5 years later he became Head of the Department of Pharmacology and Clinical Pharmacology. He subsequently spent 4 years as the Dean of Research and Development at St. George’s. He served on Wellcome and British Heart Foundation grant panels, was chair of a Higher Education Funding Council Basic Medical and Dental Science Research Assessment Exercise panel and non-executive director at St. Hellier's Healthcare Trust. He was a member of the British Pharmacological Society, Physiological Society, Biophysical Society, Save British Science, Biochemical Society, University Federation Animal Welfare and Royal College Veterinary Surgeons. In 1998 he was elected to Fellowship of the Academy of Medical Sciences and the Academia Europaea in recognition of his outstanding contributions.

Tom built a world-leading smooth muscle research group. “The Smoothies” specialised in investigating ionic events and associated ion channels of smooth muscle cells. These cells quietly, subconsciously but critically determine movements of fluids and substances in tubes and containers throughout the body. Tom’s group was in the vanguard of research that utilized new technologies – single cell patch clamp electrophysiology, laser confocal imaging - and he established many international collaborations as a consequence. He was a master of the single and double sucrose gap techniques and hand-built some of his lab’s early patch clamp equipment. In the autumn of 1981, he returned from a lecture tour with a small brown envelope. He had been to A.M. (Buzz) Brown's lab in Texas where he had been given two 1GΩ resistors, which were essential components of the patch clamp head stage and difficult to get hold of. The equipment Tom then built was used to make many published patch clamp recordings from smooth muscle cells until commercial amplifiers became available. The lab was truly pioneering.

Tom was especially interested in ionic events evoked by acetylcholine acting on intestinal smooth muscle cells to regulate gut motility. He described membrane depolarizing effects (Bolton, 1971, 1972) and used microelectrodes and voltage clamp to further characterize them (Bolton, 1975). He applied newly emerging patch clamp and cell isolation techniques to prove that underlying the depolarization was a non-selective cationic transmembrane inward current (Benham *et al.*, 1985). He showed the relationship with intracellular calcium concentration (Pacaud & Bolton, 1991), roles of G proteins (Komori & Bolton, 1990) and types of muscarinic receptor (Zholos & Bolton, 1997). He revealed the voltage dependence of the ionic mechanism and pointed to involvement of non-selective cationic channels that are now known as Transient Receptor Potential or TRP channels (Zholos *et al.*, 2004). He showed that several principles were relevant to the actions of other transmitters such as noradrenaline on arterial smooth muscle cells (Bolton *et al.*, 1984). He inspired the field with seminal review articles on the mechanisms of action of transmitters and other substances (Bolton, 1979) and excitation-contraction coupling (Bolton *et al.*, 1999) in smooth muscles.

Tom and colleagues recognised that the depolarizing effect did not occur in isolation. His team identified spontaneous transient outward currents (STOCs) (Benham & Bolton, 1986), properties of calcium stores (Bolton & Lim, 1989) and calcium release events induced by inositol 1,4,5-trisphosphate (Komori & Bolton, 1991). He introduced new calcium imaging techniques to observe the calcium events and their subcellular distribution in real-time (Imaizumi *et al.*, 1998) and crosstalk between different intracellular calcium-release channels (Gordienko & Bolton, 2002). Tom and his team combined confocal laser scanning microscopy with simultaneous patch clamp recordings for direct visualization of subcellular calcium signalling acting at ion channels, developing a “local calcium control” concept (Gordienko *et al.*, 1999) that built on the original STOC observations[12]. Spatial organisation of the calcium in endoplasmic reticulum and mitochondria was revealed (Gordienko *et al.*, 2001).

His group described depolarization-activated calcium currents (Aaronson *et al.*, 1988) and the counterbalancing potassium channel mechanisms. As such his group was one of the first to characterise calcium-activated potassium channel (Benham *et al.*, 1986) and delayed rectifier potassium channel currents in smooth muscle cells (Beech & Bolton, 1989). Tom’s group identified two types of adenosine triphosphate-sensitive potassium channel in smooth muscle, one of which was activated by nucleotide diphosphates (Beech *et al.*, 1993; Zhang & Bolton, 1996), and a hyperpolarization-activated current mediated by potassium and sodium ions (Benham *et al.*, 1987). His group was amongst the first to describe endothelial-dependent hyperpolarization regulating adjacent smooth muscle cells (Bolton *et al.*, 1984; Bolton & Clapp, 1986) and recognize interstitial cells in the vascular wall (Povstyan *et al.*, 2003; Pucovsky *et al.*, 2003). His interests extended to eosinophils, in which his team characterized proton currents (Gordienko *et al.*, 1996). Tom was known to roll up his sleeves and fearlessly perform venepuncture on himself to donate blood for the experiments!

In 2005, there was celebration of Tom’s scientific contributions with a Physiology Society meeting in Oxford, bringing together investigators from across the world. In 2011, he was awarded an Honorary Doctorate from Kingston University in recognition of his outstanding contributions and development of teaching. At the ceremony, he said "I would say there are no short-cuts. Understand everything you do 100 per cent at each and every stage, be prepared to work long hours, be almost zealot-like in your approach, learn how to fight off bureaucrats - only then will you have the drive and knowledge to succeed." Those who knew Tom will recognise his character from this statement and remember him fondly. As a PhD student working in another institution was once told “practise your talk well because Tom Bolton is likely to be present’”. He was a yardstick of quality. He valued thoroughness and, above all, critical straightforward thinking, and tolerated no nonsense.

Many of the people who trained with Tom went on to senior positions across the globe fuelled by his relentless work ethic. Investigators inspired by him and whom he supported in many ways were from countries including Australia, Bulgaria, China, France, Germany, Japan, Slovakia, Ukraine and USA. He inspired the next generation of investigators, many of whom were very fortunate to have worked with him, and so the research goes on, but his energy and contributions will be missed.

Tom was a ferocious competitor on the squash court and 5-a-side pitch, especially when his eyes had gone a bit - ouch! He was a keen weight lifter, lover of fast driving in high-end cars, which he serviced himself, and big fan of curries. A do-it-yourself enthusiast, he repaired, improved and extended his house in South Nutfield. He also had an old tractor, which he used to mow the grass in the field where his rather intimidating Dobermann Pinscher dogs could exercise. With up to five of them in the house, it could be difficult to find a place to sit. Pat (née Moore, whom he married in 1961) exhibited the dogs at Crufts. Fairly recently he hired, and learned to operate, a digger, just in order to bury one of his dogs on his property He was indefatigable in battling against any authority, including water companies, banks, hospital trusts and social services.

Pat died in 2017 and his second son Nicholas in 2008. Tom is survived by his sons Grant and Kirk and five grandchildren.

Tom passed away after a short illness on 27 May 2024.

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