

In Memoriam: Sidney George Shaw, D Phil (1948-2017)

Matthias Barton,^{a*} Hilary J. Little,^b Richard D. Vaughan-Jones,^b
Stephen Daniels,^b Michael R. Dashwood,^c Janice C. Tsui^{c*}

^a University of Zürich, Switzerland, ^b Oxford University, United Kingdom,
^c University College London, United Kingdom

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* Address for correspondence:

Matthias Barton, MD, FAHA, FESC
University of Zürich
Molecular Internal Medicine
Y44 G22
Winterthurerstrasse 190
CH-8057 Zürich
Switzerland

Phone +41-77 439 5554
barton@access.uzh.ch

or Janice C. Tsui, MD, FRCS
University College London
Division of Surgery and Interventional
Science
Royal Free Campus
London NW3 2QG
United Kingdom

Phone +1-214-648 5082
janice.tsui@ucl.ac.uk

Abstract

On March 4, 2017 at the age of 68, Sidney George Shaw (Sid) unexpectedly died from complications following surgery, only four years after retiring from the University of Bern. Trained in biochemistry at Oxford University, Sid had quickly moved into molecular pharmacology and became a key investigator in the field of enzyme biochemistry, vasoactive peptide research, and receptor signaling. Sid spent half his life in Switzerland, after moving to the University of Bern in 1984. This article, written by his friends and colleagues who knew him and worked with him during different stages of his career, summarizes his life, his passions, and achievements in biomedical research. It also includes personal memories relating to a dear friend and outstanding scientist whose intellectual curiosity, humility, and honesty will remain an example to us all.

«We are here to add what we can to, not get what we can get from, life»

Sir William Osler, Regius Professor of Medicine at Oxford University (Osler)

The above quote by Canadian physician Sir William Osler (1849-1919) undoubtedly gives a good summary of the working ethos that Sidney "Sid" George Shaw (**Figure 1**) followed his entire life. On March 4, 2017 at the age of 68, Sid unexpectedly died from complications following surgery a few weeks earlier, and only four years after retiring from the University of Bern. Born in Liverpool and trained in biochemistry at Oxford University, Sid quickly moved into molecular pharmacology. He spent half his life in Switzerland, after moving to the University of Bern in 1984. There, he became a key investigator in the fields of enzyme biochemistry, vasoactive peptide research, and GPCR signaling and function. In this article, his friends and colleagues who knew him and worked with him during different stages of his career, summarize his life, his passions, and achievements in biomedical research. The article also includes personal memories relating to a dear friend and outstanding scientist whose intellectual curiosity, humility, and honesty will remain an example to us all.

Early life and education in Liverpool

Sid was born on September 25th, 1948, and received his schooling in the city of Liverpool in the North of England. Liverpool at the time was a lively town with the new pop music that began and flourished in that area of the country, and the youth culture that developed in the sixties. As a teenager Sid enjoyed both the music and the social scene, growing up in the city that gave the world the Beatles. A more contemplative pastime that Sid also discovered in those days was fishing, which he continued to pursue throughout his adult life.

D. Phil at Oxford University

Sid went up to Oxford University in 1968 to read biochemistry at Queen's College. Oxford in those days was not the easiest of places for a state-school boy from the north of England, societal differences were considerably greater than they are now, but Sid soon settled into the University's lively social and academic scene. Stephen Daniels, who was from Manchester, and Sid became close personal friends, sharing the fact that at Oxford they were "outsiders" from the North, albeit from different ends of the East Lancs Road. They first met at the Oxford Underwater Exploration Group (diving club) in 1970. Sid lost interest but it became a major interest in Stephen Daniel's life. Both remained in the Pharmacology Department until 1984 when Sid left for Switzerland and Stephen Daniels moved to Physical Chemistry.

After completing his first degree in 1972, Sid spent two years working as a research assistant with psychologist and neuroscientist Dr Edmund T. Rolls in the Experimental Psychology Department at Oxford University. This was something of a change of academic direction for Sid, moving from biochemistry to *in vivo* studies on the effects of brain stimulation on behaviour, but his time there was prolific, resulting in the publication of several papers in prestigious journals (Rolls *et al.*, 1974a; Rolls *et al.*, 1974b; Mora *et al.*, 1975; Shaw & Rolls, 1976). In the same year, at the age of 24, Sid married his first wife, Mary, and they had two sons, Owen and Andrew (**Figure 2**).

Neurobiochemistry and neuropharmacology

In 1974, Sid moved to the Pharmacology Department in Oxford, to read for a D Phil under the supervision of Dr Bill Cook, supported financially by a Medical Research Council Studentship. He completed the degree in 1978 (**Figure 1**). The topic of his doctoral thesis was "Studies on peptidase enzymes in the central nervous system", which was the start of a long and productive time for Sid working in enzyme biochemistry. His doctoral work resulted in a paper published in *Nature* in 1978 (Shaw & Cook, 1978), as well as in other publications (Shaw & Cook, 1979). He demonstrated the selective localisation of arylamidases to specific cells and regions in the mouse CNS, and showed that seven different aminopeptidase enzymes, not previously demonstrated, could be identified in brain. His studies also highlighted, and solved, the

difficulty of distinguishing between neuronal and vascular locations of the enzymes. These studies, and his later work, helped to lay the foundation for what is now an extensive area of research on the regulation of peptide activity in the brain. Stephen Daniels also made use of Sid's analytical abilities which resulted in a shared publication in the Proceedings of the «Undersea Medical Society» (Daniels *et al.*, 1981).

The Oxford Pharmacology Department in those days was very active, both scientifically and socially, with a group of DPhil and postdoctoral researchers who (unusually) all came from the same relatively small area in the north of England. These included Stephen Daniels, Richard Vaughan-Jones and Hilary Little, with whom Sid became life-long friends. Conversations were lively and constructive, with key experiments planned, either over coffee in the Department or in local pubs in the evenings, notably the “Royal Oak” on the Woodstock Road and the “Lamb and Flag” on St Giles. The former was opposite the original Radcliffe Infirmary, where the use of penicillin was first developed in the 1940s and 1950s, and so patrons at the pub would also include young clinicians and hospital workers. Sid was typically the life and soul of his social group.

Following his D Phil (**Figure 1**), Sid spent several more years in the Pharmacology Department at Oxford, interrupted by a brief spell at the University of Grenada in Spain as a Visiting European Neuroscience Foundation Fellow. Sid's work in Oxford was supported firstly by the Medical Research Council and then the Wellcome Trust, enabling him to extend his investigations of peptidase enzymes, resulting in several more valuable publications.

In 1982, the Pharmacology Department of Oxford University celebrated its 70th anniversary, and to mark this event Sid and other researchers presented a Comedy Review that included Sid accompanying himself on guitar with a self-penned song entitled "Pharmacology's Growing". This contribution was particularly appreciated by Department-head, Professor Sir William Paton. Sadly, in those days, video recordings were not a simple matter of using one's mobile phone, so no record of his great performance in this Review exists, except in our memories. But the event emphasizes

that Sid's extracurricular activities, particularly in folk music, were as lively and original as his contributions to scientific research.

Another anecdote is from the British Pharmacological Society's 50th Anniversary Meeting in Oxford in 1981 organized by Sir William Paton (1917-1993)(Hall, 1994; Rang, 1994; Rang & Lord, 1996) where Sid served as a door guard: Sid refused entry to Marthe Vogt (1903-2003) - one of the leading neuroscientists of the 20th century who contributed to the work that won Sir Henry Dale the Nobel Prize in Physiology or Medicine in 1936 (Dale; Dale *et al.*, 1936) - until she found some ID. Oxford's Professor of Pharmacology, Edith Bülbring (1903-1990) another world-renowned scientist (Born, 1985; Bolton & Brading, 1992), was furious but Marthe Vogt complimented Sid on his diligence.

It was during Sid's later years in Oxford that he met Jane, at the time a chemistry project student of Stephen Daniels undertaking a 12 month research project in the Department. Following his divorce, Sid and Jane became romantically linked. Indeed, they were inseparable as a couple, and remained so for the rest of Sid's life.

Vasoactive peptides and endothelin research

Sid and Jane left Oxford in 1984 (**Figure 2**), travelling to Switzerland to work with Peter Weidmann at the University of Bern. They grew to love the country, its mountains and lakes, and settled there permanently. In the first decade, Sid's scientific focus was directed towards renal pathophysiology and the role of the then newly discovered atrial natriuretic peptides, including urodilatin. The research also branched into clinical work, with seminal studies conducted in human volunteers and in patients. (Weidmann *et al.*, 1986a; Weidmann *et al.*, 1986b; Shaw *et al.*, 1987; Ferrier *et al.*, 1988; Saxenhofer *et al.*, 1990)

At the same time, the role of the endothelium in the regulation of vascular tone had become a most active area of research in cardiovascular medicine, and in 1987 nitric oxide was identified as an endothelium-dependent vasodilator - a discovery that was awarded the Nobel Prize in Physiology or Medicine in 1998. (Zetterström, 2009). Also in

1987, Masashi Yanagisawa, Katsutoshi Goto, Tomoh Masaki and coworkers (Barton *et al.*, 2012a) identified peptide and gene sequences of a group of endothelium-derived vasoconstrictor peptides which they designated endothelin to reflect its endothelial cell origin. (Yanagisawa *et al.*, 1988) At the time, measurements of endothelin were limited to circulating levels in plasma, with elevated levels reported in patients suffering from heart failure, atherosclerosis, renal diseases, and diabetes. (Rubanyi & Polokoff, 1994) The role and regulation of tissue endothelins was entirely unknown. This was largely due to their very low levels. As a result, the quantification of local concentrations could not be achieved in small tissue samples.

In 1995, Matthias Barton, also moved to the University of Bern's Division of Cardiology as cardiology fellow working on coronary artery disease and atherosclerosis. His research included studying functions of endothelial cell-derived mediators, including endothelin. Since, in many pathological conditions, circulating levels of any vasoactive peptide or hormone can be normal in plasma yet elevated in tissue, Matthias Barton hypothesized at the time that cardiovascular pathologies and therapies might affect production and thus local concentration of endothelin in tissue - even if plasma levels remain largely unchanged. But there was no method to test this hypothesis.

Matthias Barton learned that Sid had just published the measurement of plasma levels of the peptide (Goerre *et al.*, 1995). They met and he explained his "local endothelin system" hypothesis to Sid and that a specific, high-sensitivity assay allowing reliable quantification of endothelins from very small amounts of tissue would be needed to test it. Expecting to hear that this would be impossible, Sid smiled and said: "Let me try something".

Quickly the first tissue samples arrived and Sid and Jane began to work on them immediately, using radioimmunoassay and HPLC techniques. Sid obtained some data from the homogenized tissue but the yield was low and measurements were quite variable. Matthias Barton then came to Sid's lab to introduce a new method he had previously used during his D.M. thesis work (Mügge *et al.*, 1993a; Mügge *et al.*, 1993b). Extraction of endothelins from pulverized snap-frozen tissue not only resulted in higher

yields but also added much to the precision of the assay. Sid smiled and was very happy: he knew that he now had the first assay in his hands that would allow reliable quantification of tissue endothelin levels with very high sensitivity and specificity. Within weeks, he and Jane had extracted and measured numerous samples from studies that were ongoing at the time, establishing the first high-sensitive and specific ET-1 tissue assay, demonstrating for the first time that cardiovascular and other diseases lead to pronounced activation of the tissue endothelin system. Without doubt, many of the resulting papers published over the next two decades were achieved in part because they contained data generated with Sid's ET-1 assay. (Barton *et al.*, 1997; Barton *et al.*, 1998; Barton *et al.*, 2000; Vetter *et al.*, 2006)

Sid was soon approached by others wishing to include his new method in their applications for research funding. He quickly sensed that he might become exploited and lose control over the technique he had pioneered. On October 13, 1998, Sid wrote in an e-mail to Matthias Barton: *"It was never intended they [the methods] should be included as a whole in any other grant. [...] We spent 3 months developing this molecular biology methodology and there is no way I am handing any details to anyone. The crazy thing is that there must be now several grants submitted which all depend to an important extent on my tissue ET and NO methodology. The problem is we are getting no credit for it and more importantly none of the grants include any request for technical support for this lab (basic costs are one thing but a 20% technician for example would help considerably. [...] We have an edge which nobody else has and I am not prepared to risk it."* Although Sid ended up publishing a large number of articles employing the method he had invented, in the end - as he already felt in 1998 - he did not receive the credit and recognition that he deserved. It is without doubt that the tissue endothelin assay that Sid invented has immensely contributed to endothelin biology, and helped our understanding of intracrine and local effects as well as the regulation of the endothelin system in health, disease, and following therapeutic intervention.

Brain corticosteroids and alcohol research

In addition to his research in the vasoactive peptide field, for the last 20 years Sid also collaborated with Hilary Little, a psychopharmacologist from the Oxford Department, on

a research project on brain corticosteroids. This project arose from a chance conversation when they met at a reunion. The research involved measurements of concentrations of glucocorticoid in different brain areas, and the effects of prolonged alcohol consumption. This had never previously been examined, as the assumption had been made that the brain levels simply followed those in plasma. Sid's broad biochemical experience allowed him to devise reliable methods for the separation, assay and localisation of brain glucocorticoids. These *in vivo* studies demonstrated prolonged location-specific increases in glucocorticoid levels following withdrawal from chronic alcohol consumption, which may be involved in relapse drinking in abstinent alcoholics (Little *et al.*, 2008; Rose *et al.*, 2010). Hilary Little relates that Sid was a wonderful colleague providing both expertise and support, both when they successfully applied for research grants and published papers, and when, as in all research, when things did not go entirely to plan.

Peripheral vascular disease and inflammation immunology

In March of 1998 a Symposium on Endothelin Antagonism was held at the University of Zurich where Matthias Barton had moved the year before (Gross & Bussemaker, 1999). Here Mick Dashwood and Sid first met, and they discussed areas of mutual interest. In the 1970s both were independently involved in projects on the role of monoamines and opioids in brain stimulation-reward mechanisms, Sid at Oxford and Mick Dashwood at the National Institute for Medical Research in north London (Dashwood & Feldberg, 1978, 1980; Shaw *et al.*, 1984). Also, at a personal level, they shared similar musical tastes of that era, particularly the guitar heroes of the day. As mentioned earlier, Sid was a keen guitarist (**Figure 3**).

After getting together a couple of times it became clear that they shared similar research interests and research began to develop in both directions. Soon, Sid's son, Andrew, brought to Bern samples from clinical studies in London, to be processed in Sid's lab (Dashwood *et al.*, 2009). Sid also visited the Royal Free Hospital, one time bringing with him frozen samples from a diabetes study, neatly prepared in aluminium chocolate cups! A week was spent frantically sectioning and NADPH-diaphorase staining, with results that were equally quickly published (Balsiger *et al.*, 2002).

Mick Dashwood has many memories of times with Sid, meeting up and socialising at various international scientific conferences. Sid missed English beer, after many years of living in Switzerland, so they would often tour various pubs in the Hampstead area during his visits to London, his favourite being the Magdala, sadly now closed. One memorable get-together was when Sid arrived at the Royal Free about two hours later than planned with his son Andrew, both wearing dark suits and black ties. Andrew was a TV cameraman at the time, and was involved in covering the Queen Mother's funeral. Accompanied by the two 'men in black' Mick Dashwood went to enjoy a few beers. All this before meeting Janice Tsui who was treating the three to a 'thank you' French/Thai fusion meal at one of her favourite gastro eateries in Soho. An evening to remember.

Janice Tsui, at the time a vascular surgery fellow at London's Royal Free Hospital working on her MD thesis studying peripheral vascular disease, first met Sid in 2000 when she took a trip to Bern with a collection of muscle biopsy samples to be processed for the various molecular techniques available in Sid's lab. During this two week trip, long hours of concentrated bench work were followed by enjoyable evenings out at local restaurants discussing science, family, music, travel and other passions in life. This was the start of a continued collaboration, looking at the inflammatory pathways in ischaemic skeletal muscle (Patel *et al.*, 2012; Spirig *et al.*, 2012; Navi *et al.*, 2013), as well as a firm friendship. Sid and Jane continued to host young surgeons from London in Bern during this time. Sid was an inspirational mentor not only in science but also in his passion to enjoy every day with all those around him. Sid and Janice Tsui got to know each other's families and made the most of collaborative meetings to meet up. During that time, Sid and Jane finally tied the knot and got married at the beautiful Schloss Spiez close to Lake Thun in Switzerland in August 2007 - 25 years after having first met each other (**Figure 4**).

Remembering Sid

Sid became an active figure in the endothelin field attending its research conferences, including the Eleventh International Conference on Endothelin in Montréal in 2009; he joined the organizing committee and was a session chair (**Figure 5**) at the Twelfth

International Conference on Endothelin in Cambridge in the following year (Barton, 2012; Barton *et al.*, 2012b). In the same year, Sid co-organized the "International Workshop on the Endothelium in Health and Disease" in London together with Mick Dashwood, Matthias Barton, and David Abraham, the conference proceedings were later published as a book (Abraham & Dashwood). Over the years, Sid had received prestigious grants, awarded by the Swiss National Science Foundation supporting his research. Sid retired from his position as Head of the Vasoactive Peptide Research Group at the University of Bern in 2013.

Sid supported Janice Tsui in hosting the Royal Free International Cardiovascular Workshops between 2009-2011 and was involved in the European Society of Vascular Surgery Spring meeting in 2013 in Frankfurt (Navi *et al.*, 2013) and in 2014 in London (**Figure 6**). Indeed, Sid invited Richard Vaughan-Jones as a scientific speaker at one of the Royal Free Workshops, thus reinforcing their long friendship after a lapse of several years. Richard Vaughan-Jones recounts that he was grateful for this, as it prompted a recent holiday weekend with Sid and Jane in Dorset, where memories of the Oxford Pharmacology Department were exchanged, friends recalled, and guitar music once again played late into the night. The occasion was a timely book-ending of careers in science.

Sid loved life, and lived it to the full, both scientifically and socially. In the years following his retirement he and Jane (**Figure 7**) had begun travelling all over Europe, and were planning to do so in the years to come. Fate had it that this was going to happen only for a few years, which Jane fondly remembers.

According to Jane, Sid had one true goal in his work: "*What Sid wanted was to further science. He was not interested in politics or power play.*" The former, perhaps the highest goal any scientist should pursue, sometimes got Sid into trouble with others more interested in the latter. It meant so much to Sid that he and his colleagues had been able to bring new medical treatment approaches all the way from the first ideas and the laboratory studies to the clinic where they are making a difference to peoples' lives. Sid was one of the most intellectually curious scientists we have ever met. He was

a humble, honest, and warm-hearted man (**Figure 8**) who so much loved what he was doing ,He will remain an example for all of us, we remember him both as a scientist and as a warm, outgoing and loyal friend. Our feelings are with his wife and his children. We, his friends, mourn that his life was cut short far too early.

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Figure Legends

Figure 1

Left: Picture of young Sid Shaw at the age of 28, taken in 1976 in Oxford. Right: Sid in his D. Phil gown of Oxford University after the thesis ceremony 1978. The was taken at the celebration of Sid's degree which he shared with Stephen Daniels and was at the Royal Oak pub in Oxford; after they had drunk all the champagne they rushed off in their finery to find an off-licence with more. Photographs by Hilary Little and Jane Shaw-Boden

Figure 2

Sid on his last day at the Department of Pharmacology at Oxford University in 1984. Also pictured are his sons Owen and Andrew. Photograph by Jane Shaw-Boden.

Figure 3

Sid's son Andrew and Sid playing guitar together at their home in Spiez, Switzerland. Photograph by Jane Shaw-Boden.

Figure 4

Sid at his own wedding on 3 August 2007 at Schloss Spiez, Switzerland. Photograph by Hilary Little.

Figure 5

Sid at the International Conferences on Endothelin, an area of research which he helped advance by pioneering the precise quantification of tissue concentrations of endothelin peptides from very small tissue samples. Above: Sid in 2009 taking notes during the ET-11 meeting held in Montréal, Canada, held in September. Also pictured is Pierre Moreau, at the time at the Université de Montréal, who in the mid-1990s was a post-doctoral fellow at the University of Bern where he also worked with Sid. Below: Sid in 2011, chairing a session at the ET-12 meeting in Cambridge, UK, together with Yasuo Matsumura, Osaka University, Japan. Photographs by Matthias Barton and Suzette Sandin.

Figure 6

Jane and Sid by Lake Thun near Spiez in 2011. Photograph by Hemanshu Patel, Research Fellow in Janice Tsui's group, taken during his visit in Bern.

Figure 7

Sid with Jasper, Janice Tsui's son, who was 13 months at the time: clearly enjoying lunch at a Spanish restaurant in London after the European Society of Vascular Society Spring Meeting in May 2014. Photograph by Janice Tsui.

Figure 8

Jane and Sid at a friend's wedding in 2016. Photograph by Jane Shaw-Boden.