



In memoriam, Roy Weller (1938–2022)

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On 23rd August 2022, Roy Weller BSc MD PhD FRCPath, Emeritus Professor of Neuropathology in the Faculty of Medicine, University of Southampton, UK sadly passed away. I first met Roy Weller in his office in Southampton General Hospital in 1999 after I had taken up an academic teaching position in Anatomy. I wanted to explore with him what he thought the consequences of the brain not having lymphatic vessels are. He sat me down and showed me a case of cerebral amyloid angiopathy. The discussions that followed fueled my desire to discover why a protein that we all produce and need for the normal function of our synapses deposits in the walls of cerebral capillaries and arteries. Together with Hugh Perry, we constructed the experimental plan of how to test the hypothesis that drainage of solutes from the extracellular spaces of the brain occurs along the basement membranes of capillaries and arteries as Intramural Periarterial Drainage (IPAD). I embarked on a PhD supervised by Roy Weller and Hugh Perry and exciting times began. The attention to detail that Roy had for experimental setup as well as reporting the results and writing up was extraordinary. For those of us supervised, trained or taught by him, the degree of how much red pen was on our manuscripts became the subject of competition. He became my mentor at a time when I was working full time teaching medical students anatomy, while undertaking a PhD, pregnancy and two children. There are many unique memorable moments that his colleagues, trainees, students, mentees have had with Roy, but not many will be able to say that they were writing chapters of their thesis while breastfeeding and with their supervisor present, encouraging and helping along with the writing. Throughout the spectrum of highs and lows of professional and personal life Roy Weller was

there, checking, offering not just advice, but help. He did not just open doors, he would push me and others through them. Then came the challenge of our research being questioned by the newer theories of glymphatic drainage. While I applied my Latin temperament of high emotive state, he took this on with determined calm and dignity. With funding from Biogen, in 2017, we designed and performed new experiments that showed clearly that drainage of soluble amyloid-beta from the cerebral parenchyma occurs along the basement membranes of capillaries and arteries. When injected in the cerebrospinal fluid, soluble amyloid-beta entered the brain within 5 min along the glymphatic pathway of the basement membranes of the perivascular compartment of arteries (glia limitans and pia mater) and after 30 min, the amyloid-beta was found in the IPAD pathway. “Even more exciting” he said.

In his words, we cut the umbilical cord in 2008 when I managed my first project grant and Cheryl Hawkes very accomplished senior postdoctoral fellow joined our group, but he was never far away. He would come to our lab meetings and was excited about our new results. He encouraged interdisciplinary work and was fascinated by the discussions on mathematical, physical or computer science modeling. Traveling to conferences with him was fun, as he loved introducing people to each other and encouraging collaborations. When he could not travel any more, we were discussing the new findings, people, presentations that I had come across. I lost my mentor but his working hypotheses and philosophy of life will continue to guide me.

Roxana Carare

It was a great pleasure to know Roy, he was a charming person, a fountain of knowledge, very generous with his time and wonderful company when discussing matters scientific, historical or whatever was the topic at the time. When I arrived in Southampton, he was a great colleague, he was very supportive and offered useful advice on many occasions. I recall conversations perched on a chair in his office among seemingly endless boxes of slides discussing

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Fig. 1 Roy Weller, flanked by (left to right) Henryk Wisniewski (Staten Island, NY), Taihei Miyakawa (Kumamoto, Japan), Mrs Miyakawa, Mrs Meyer, Blas Frangione (NY), John Meyer (Houston, USA) and Raj Kalaria (Newcastle upon Tyne, UK), 1999



everything from nuances of neuroimmunology to how to deal with vagaries of university life and much else besides.

I consider myself fortunate to have shared times with Roy as will all those who knew him.

Hugh Perry

I had the pleasure to meet Roy Weller for the first time in London in July 1994, when he organized an international symposium to mark the retirement of Michael Bradbury. At that time, I was a junior group leader at the Max Planck Institute for Physiological and Clinical Research in Bad Nauheim, Germany in the department of the late Werner Risau. At this meeting, Roy Weller gave me the opportunity to present my



Fig. 2 Roy Weller, with (left to right) Fabrizio Tagliavini (Milan, Italy), Mike Shelansky (NY, Columbia) and Thomas Wisniewski (NYU, NY), 2014 (courtesy of Leila Chimelli)

work on the role of endothelial adhesion molecules mediating *T* cell migration across the blood–brain barrier into the CNS. His question if and how *T* cells would also leave the CNS initiated a lively exchange of data and inspiring discussions about ideas between us and eventually led to a review article entitled “Lymphocyte Targeting the CNS: A review of afferent and efferent CNS immune pathways” that was published in *Brain Pathology* in 1996. He further supported my career by inviting me to the Wye College Neuropathology Meeting in 1997, where I had the chance to interact as junior group leader with the “Who-Is-Who” in international neuropathology and, thus, build a network in this community. I, thus, grew to admire and appreciate Roy Weller as a curious, patient, thoughtful and always supportive mentor. In our continuous interactions I came to appreciate him as an excellent clinical neuropathologist, meticulous researcher and painstaking observer. I readily grew as a fan for his characteristic “artful communication” by always making a drawing of the concepts as discussed, a predilection I do share with him.

In light of the more recent rediscovery of the dural lymphatic vessels and the publication of the “glymphatic hypothesis” our discussions on the efferent and afferent pathways of CNS immunity were reignited and now as an established researcher it was again a distinct pleasure for me to make use of Roy Weller’s lexical knowledge and his love for details allowing us to write two additional reviews on “Vascular, glial, and lymphatic immune gateways of the central nervous system” published in the *Acta Neuropathologica* in 2016 and on “The movers and shapers in immune privilege

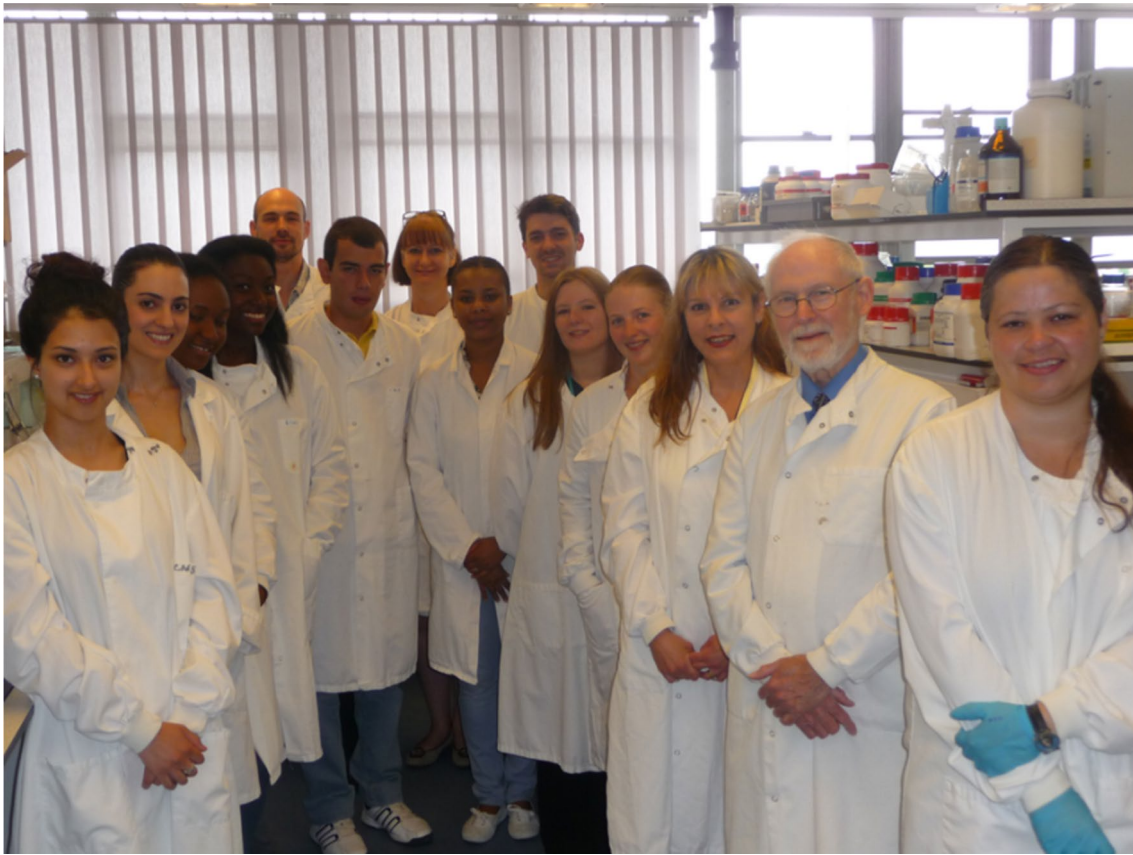


Fig. 3 Roy Weller next to Roxana Carare, Cheryl Hawkes and the rest of the IPAD research group

of the CNS” published together in *Nature Immunology* in 2017 that both aimed to provide a balanced overview of the field integrating the previous knowledge into the new concepts. The COVID-19 pandemic prohibited his travel to the Theodor Kocher Institute at the University of Bern, which I am directing since 2003 and, thus, my wish to introduce him to my staff in person. Dedicated to be available for a seminar talk and discussion with us at the TKI, he mastered a Zoom Seminar from his home in May 2020 and inspired the next generation of researchers with his presentation, knowledge and curiosity for their questions and research work.

With Roy Weller, we lose an inspiring clinical researcher, teacher and mentor. He made outstanding contributions to our current understanding of brain fluid flow in the correct context of the brain barriers and brain anatomy. I will deeply miss him as a gentle and humble colleague and friend as well as a role model because he was a patient and curious listener, an excellent observer, and an open-minded thinker.

Britta Engelhardt

I first met Roy Weller at what were the summer meetings of the British Neuropathological Society (BNS) in the late 1980s. I had learnt of Roy’s elegant research on lymphatics

of the brain and use of India Ink to trace these pathways in rodents. That captivated me especially as I was learning about the physiology and neuropathology of the blood–brain barrier, while I as a training fellow at Case Western Reserve University, USA. Around the same period of time, I had also reconnected with Michael Bradbury (1930–2013, *Concept of the Blood–Brain Barrier*) at King’s College London, where I had been a postgraduate student in the late 1970 s. Both Roy and perhaps needless to say, Michael were instrumental in sustaining my interests in cerebrovascular diseases and their pathophysiological mechanisms. I particularly recall Roy’s lucid talk on the process of what subsequently came to be called IPAD for *Intramural Peri-Arterial Drainage*, given at Slaley Hall in Northumberland, outskirts of Newcastle upon Tyne, where Paul Ince (Sheffield) and I hosted the *Vascular Factors in Dementia* symposium (*Kalaria RN, Ince P. (eds), Ann NY Acad Sci, Vol 903, 2000*) in May 1999. Roy’s clear explanation and discussions which followed helped me to fully comprehend the concept of drainage and aging blood vessels were really key to the retardation in protein clearance from the cerebrum. At the Slaley Hall meeting (Fig. 1), along with Roy, there were other giants of vascular pathophysiology and neuropathology including Henry M.

Wisniewski (1931–1999, *Acta Neuropathol* 98: 565–566, 1999), Taihei Miykawa (Kumamoto), Blas Frangione (New York), Harry Vinters (Los Angeles) and Marie-Magdeleine Ruchoux (France). Fortuitously too, Blas Frangione, Georg Ghiso (New York) and Thomas Revesz (London) celebrated the discovery of the cause of Abri CAA (dubbed as British Dementia) with the publication of their *Nature* paper describing the stop codon mutation in Abri at the Slaley Hall meeting. I recollect the conversation with Roy about Abri CAA and drainage. Perhaps not surprisingly, Roy's thoughts were already ticking over on the application of this discovery in relation to IPAD and how other amyloid or β sheet promoting proteins might be drained from the brain. In recent years, Roxana Carare and Cheryl Hawkes have skillfully taken forward this important research from early concepts to realities. Over the years, I can confidently recall many a stimulating and friendly discussions with wit and humor. Roy and I also sat on many committees and review panels. Always enlightening and I never went away without learning something new about our work including diagnostic clues or

how to inject new ideas in my current vascular research. He was a fountain of resourceful ideas, especially when conversations lead that way concerning the vascular field. I much enjoyed his company and looked forward to meeting Roy at the annual BNS meetings. Over the last decade, it had become a tradition to have dinner and discussion after the afternoon the special topics symposia at BNS meetings. This would obviously take place over the best Indian cuisine at a restaurant which, I would locate in London. I grew fond of Roy as a friend, teacher and mentor. He was a gentleman and a scholar (Figs. 2, 3), and he is a great miss! More expressions of appreciation will be found in *Free Neuropathology* 2:27 (2021)—Roy O. Weller <https://doi.org/10.17879/freeneuropathology-2021-3634>

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