Dr John Morley, BSc, PhD, FRCPath

Dr John Morley sadly passed away on 2nd December 2023. John was born in Filey in North Yorkshire in 1938. He was educated in Filey and Bridlington and excelled at both science and sport, especially rugby football which he continued to play into adulthood where he played in the back row for University College London (UCL) First XV and for Wasps. John obtained 4 A-levels before studying for a BSc in Zoology at UCL, a subject that was to have a profound influence on his later scientific career. Following his BSc, John obtained a PhD at UCL under the supervision of Professor Mel Schachter working principally on the regulation of blood flow in salivary glands. 'Functional hyperaemia' describes the increase in blood flow that accompanies increased salivary secretion. At the time, Sydney Hilton and Graham Lewis hypothesised that the enzyme kallikrein was released in the gland and cleavage of its substrate released the vasodilator, bradykinin. This was strongly contested by Mel, John and colleagues who provided evidence that vasodilator transmitters released from nerve terminals were more important. Graham Lewis, a co-discoverer of bradykinin, had to be prepared for fierce questioning from John whenever he gave talks on the subject.

After he obtained his PhD John spent a year in Stanford University. On returning to London John obtained a Fellowship at the Kennedy Institute of Rheumatology funded by the Arthritis and Rheumatism Council. Here he decided to specialise in the study of mediators of microvascular changes in inflammation, which was to become his life-long interest and provide the spark for the careers of many young scientists. With his first PhD student, Tim Williams, he developed sensitive techniques to measure plasma leakage from venules resulting in tissue oedema. John contributed his knowledge of oedema in a study by the Head of Immunology at the Kennedy, Dudley Dumonde, on the properties of a newly-discovered factor produced by lymphocytes that was published in Nature in 1969 (1). Dudley proposed the term 'Lymphokinin' for this factor. John strenuously contested this proposal, pointing out the potential confusion with the existing kinin family. Fortunately, John won the argument and 'Lymphokine' became the subject of the paper. In the fullness of time, this was to become the grandfather of what we now appreciate are the large family of 'Cytokines' and the subfamily of 'Chemokines'. Whilst at the Kennedy John and Tim Williams discovered the ability of prostaglandins to potentiate vascular permeability induced by a range of inflammatory mediators as an important feature of acute inflammation. This work was published in Nature (2) and became a seminal paper in our understanding of the "two mediator hypothesis" explaining the induction of oedema. John's early work at the Kennedy Institute led directly to four further papers in Nature on interactions (often synergistic) between inflammatory mediators.

I first met John in September 1980 when I joined his research group as a PhD student. John had recently been appointed as the Director of the Asthma Research Council Clinical Pharmacology Unit in the Cardiothoracic Institute attached to the Royal Brompton Hospital in London and was investigating the importance of airways inflammation to the pathogenesis of asthma. At the time asthma was considered mainly a disease associated with bronchoconstriction and the concept that inflammation was important was evolving and not universally accepted. John can be considered a pioneer in this research field by highlighting the importance of both acute and chronic cellular inflammation in asthma and how inflammatory cells contributed to one of the hallmarks of this disease, namely

bronchial hyperresponsiveness. Indeed, based on his extensive experimentation, John insisted that airway hyperresponsiveness can be selective, and that a variety of different molecular endotypes can cause the clinical manifestations of asthma, not just inflammation.

Visitors to the Unit at the Brompton were often surprised by the range of innovative experimental approaches John's laboratory used to study asthma ranging from the work of Shahin Sanjar (another of John's PhD students) who developed a model for measuring mucociliary clearance, to the first automated non-invasive models for continuously monitoring inflammatory cell recruitment into the lung which I worked on for my own PhD with Bill Paul. John was one of the earliest scientists to draw attention to the important role lymphocytes played in chronic inflammation and how these cells may be of importance in asthma drawing on his earlier work at the Kennedy Institute. John's successor at the Brompton, Professor Sir Peter Barnes, aptly commented: "John Morley always gets it right." John was also a great believer in what would now probably be referred to as "translational science" whereby observations we had made in experimental animals need to be demonstrated in humans. That usually meant that the lowly PhD students would regularly be required to "volunteer" to undergo intradermal injections with various inflammatory mediators, with and without prostaglandins and other pharmacological agents. With this type of experimental approach John's laboratory confirmed not only the "two mediator hypothesis" of acute inflammation was relevant in humans (3), but also that B2 agonists were able to inhibit vascular permeability as an important pharmacological action additional to bronchodilation (3).
Whilst at the Brompton John also ran a highly innovative and successful annual week-long course on the "Pharmacology of Asthma". This course attracted delegates from far and wide, both from Industry and academia, as John invited speakers from a wide variety of fields to give talks on areas of research he predicted (and he was nearly always right) would become important in our understanding of asthma, particularly as areas that could provide targets for new treatment approaches. A good example of this was when John invited Bob Michell to talk about lipid signalling which left the majority of the Institute wondering about the relevance of this type of basic research to lung disease. However, this was typical of John's approach to science where he believed that the best discoveries were often made by learning from areas of research that were not immediately obvious to be of interest to your own research area. This approach undoubtedly started from John's time as an undergraduate and his broad interest in biology. He was an avid reader across a range of topics and an accomplished lateral thinker that influenced all of us who were privileged enough to have had the opportunity to work with him. However, this often resulted in John depositing papers on our desk about topics as far afield as parasitology and complex statistics which left most of us baffled as to why we are being asked to read them, but you soon realised that they were always important to the research we were carrying out and John was always thinking way ahead of everyone else.

John moved into the pharmaceutical industry in 1984 when he joined Sandoz in Basel, Switzerland to head up their preclinical research group working on the development of novel drugs for the treatment of asthma. However, in addition to his work leading to the development of novel drugs, John was instrumental in making the world aware of the benefits of the orally active anti-allergy drug ketotifen as a treatment for patients with asthma, an activity that was both medically and commercially a big success. His attempt to

find a replacement for ketotifen led to the development of the PDE inhibitor benzafentrine which had both bronchodilator and anti-inflammatory activity in a single drug which sadly for John had to be stopped whilst in Phase 3 clinical trials. John was also very active in drawing attention to the dangers of using regular B2 agonists for treating asthma as they were not able to inhibit inflammation, particularly when they were used as monotherapy. At the time this view was seen as highly controversial, but the current guidelines for treating asthma reflect the view that John was promulgating in the 1980s that the use of B2 agonists as monotherapy is not recommended. Whilst working in Switzerland, John worked closely with Trevor Hansel in the Asthma and Allergy Centre in Davos which provided another example of John's pragmatic approach to "Translational Science". Working with Ian Chapman and Lazzaro Mazzoni (under the watchful eye of Brian Richardson), John had hypothesised that part of the problem of using B2 agonists regularly to treat asthma was that they were racemic mixtures and his laboratory in Basel had demonstrated that the S-enantiomer of certain commonly used B2 agonists, previously thought to be inert, could actually induce bronchial hyperresponsiveness, an observation that prompted considerable debate at a meeting of the British Pharmacological Society when this work was first presented. A study involving intravenous administration of the supposedly inactive enantiomer of isoprenaline was performed in Davos, the first recipient being Trevor Hansel while studying for his PhD with John, who had to rip out the line inserted in his arm as his heart rate raced to over 160 beats a minute. During his time in Basel, worked closely with Lazzaro Mazzoni who was his Chief technician. John very quickly appreciated that in Lazzaro he had inherited a gifted experimentalist and John encouraged him to register for a PhD which he successfully completed.

John moved back to the UK in 1993 and became a successful independent consultant to the pharmaceutical industry before becoming unwell a few years ago. However, John continued to be an avid reader despite his illness and would from time to time continue to email me to ask for references he could not find elsewhere. He remained very much in touch with what was happening in the world and his memory was as strong as ever, often correcting visitors about their recollections of events past (and in true JM fashion, he was always correct). For those of us who had the privilege to work with John over many years, there is no doubt that we have all benefited from his wisdom, guidance, intellect, wit, wicked sense of humour and encyclopaedic knowledge of the biological sciences. Scientists like John come around very rarely, and the world is a poorer place with his passing. John lost his wife Pam in 2010 and leaves three children and eight grandchildren to carry on the Morley legacy.

References

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